VOLUME 104 • JULY 1959 • NUMBER 1

A.M.A. ARCHIVES OF INTERNAL MEDICINE

The Arctic—A Place To Live and Work
Alan D. Matzger

Cryptococcosis
William J. Martin, Donald R. Nichols, Hendrik J. Svien, and John A. Ulrich

Kanamycin
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The Bulbar Conjunctival Vessels in Occlusion of the Internal Carotid Artery
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Iproniazid Hepatitis
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Abnormal Hepatic Tests in Muscular Disease
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The Syndrome of Acute Disseminated Moniliasis in Adults
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Sarcoid Heart Disease
Jerome A. Gold and Philip J. Cantor

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(1) Rubin, A., and Babbott, D.: J.A.M.A. *168*:498, (Oct. 4) 1958. (2) Kinsey, A. C.; Pomeroy, W. B., and Martin, C. E.: Sexual Behavior in the Human Male, Philadelphia, W. B. Saunders Company, 1948.

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Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee.

Second-class postage paid in Nashville, Tennessee.

CHANGE OF ADDRESS: When there is a change of address, the Circulation Office of the American Medical Association should be notified at least six weeks before the change is made. The address label clipped from the subscriber's latest copy of the publication and a statement of old and new address should be included. If there is a postal zone number, it too should be included in the new address. The instructions should state whether the change is permanent or temporary.

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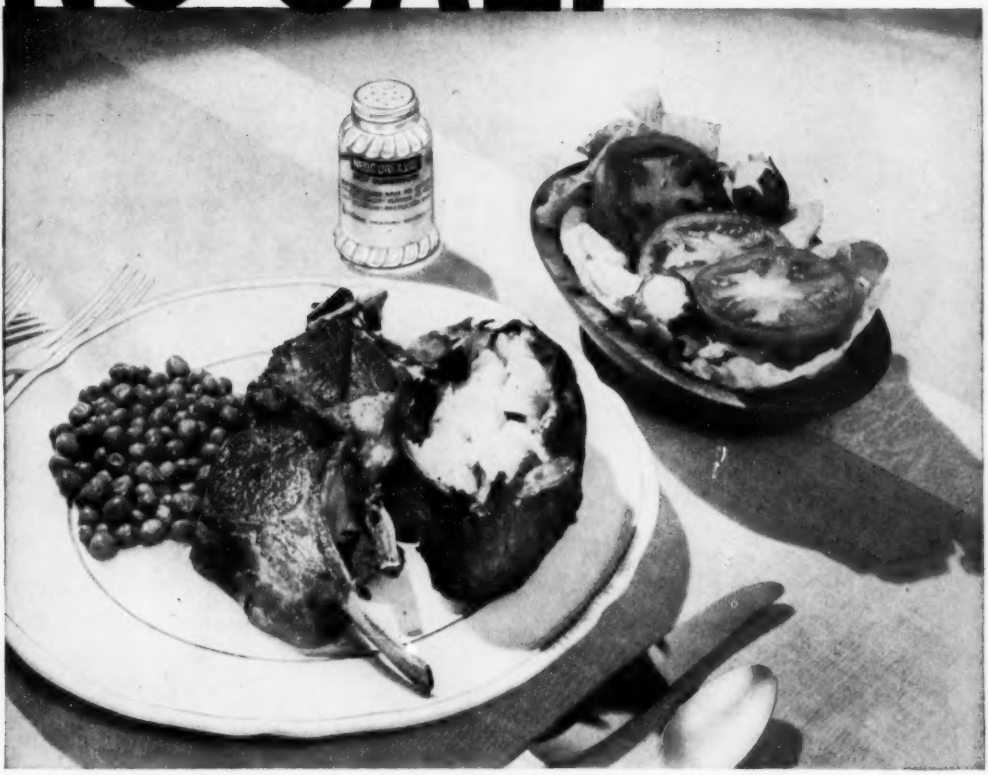

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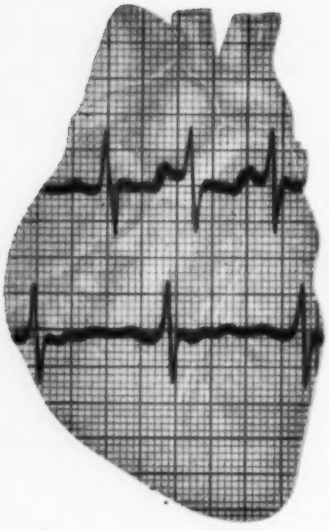

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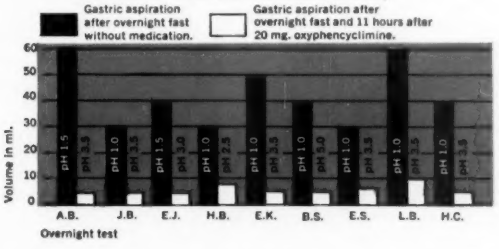

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Editorial

The Arctic—A Place To Live and Work

The awe and fear surrounding the general concept of the Arctic and Antarctic today would seem irrational. What little we know of them comes from the tales (often exaggerated for greater readability) of the heroic, intrepid explorers and hyperbolic newspaper accounts of polar activities. The most recent example of this exaggeration occurred in a comic strip concerned with Navy activities in the Antarctic. We are led to believe that harrowing episode follows upon the heels of harrowing episode—the blinding storms and white-out, tractors falling in crevasses, miserable flying conditions, and the rest. True enough, each incident was accurately drawn and each happens at the south pole as well as the north, but without the frequency implied.

But the time for our fear, based on such as that, should be behind. The experiences of ordinary people in our armed forces and in various corporations relative to polar living are making the safety and attractiveness of life in the Arctic more and more apparent.

The commercial possibilities of the far north lands are only now being explored, developed, and realized. Already Greenland furnishes the huge aluminum industry with needed cryolite.[2] Oil and uranium are being exploited in the Canadian Subarctic. That there are rich mineral deposits still farther north is most likely.

The sealing and cod-fishing industries have been established. The plentiful musk ox can provide wool, hides, and beef-like meat for the world. In Arctic Russia, wheat and other cereal grains are cultivated.

The tourist industry is still embryonic. The Danish government has only recently begun to encourage vacations in Greenland (for their citizens).[3] Their arguments for this travel have great merit: an uncommon peace pervades the island; rugged fjords indent the shore; shimmering glaciers meet the sea; unexpected fields of gaudy wild flowers dot the countryside, and the vastness of the pure white icecap is staggering. All this and more is intensified by the changing shadow patterns and colors as the sun, high in the sky at noon, roams around the horizon from north to east from evening to morning.

Greenland won't be the only "Isle of Enchantment." Certainly the islands of the Canadian and, perhaps, even the Siberian Archipelagos at some time will be open for vacationers. For those who like hot summers and still want to spend the time within the Arctic Circle, inland Alaska with its one hundred-degree temperatures (in the shade) might be just the place.

Submitted for publication March 30, 1959.

(Let the reader be cautioned not to rush to his travel agent to book an Arctic vacation. There has been no large-scale resort development. In fact, our national defense, with its high regard for the strategic position of the Arctic, precludes, for the time being, any such ventures.)

Those who pioneered the West found the Sierras almost impenetrable, but today city dwellers, without batting an eyelash, spend happy and unconcerned weeks camping there. Summertime excursions across the Greenland icecap might just fill our domesticated desires to recreate the adventures of the past; such trips will be no more dangerous than packing into the mountains.

It is seen then that sooner or later there will be considerable travel to the Arctic. The inevitable questions will arise about how the "new" environment will affect us; these come up whenever there is movement or anticipated movement into new areas. Look at today's fields of study in environmental medicine: tropical medicine, aeromedicine, and its increasingly important offspring, astronautical medicine.

A great deal, to be sure, is known (or thought to be known) about man and the cold, but still many, many questions of a fundamental nature have yet to be answered. Persons, as well as experimental animals, accustomed to cold shiver less (if at all) than the unacclimatized yet can maintain a normal body temperature; whence comes this heat? What then are the dietary caloric requirements? Higher or the same as normal? What factors aggravate the production of frostbite? Is there truly a racial predisposition, and, if so, what is its basis? Recalling that Eskimos, Arctic mammals, and even temperate-zone-loving Europeans conceive and deliver their young north of the tree line, does the cold have any effect on the course of pregnancy? Or, for that matter, on the course of any disease? Recently a physician accompanying an icecap expedition reported the development of an anemia in himself and each other member of the party; what is the pathogenesis of this disorder (if it is a disorder) and under what conditions of temperature, altitude, and diet will it occur?

The questions are endless and yet demand answering if we are to understand the polar regions as we do our temperate zone and the tropics.

Immediately, the unknowns of individual physiology are of less importance than those of a public-health nature. Water and sewage lines freeze in the winter unless the pipes are heated; the current methods of heating are estimated to cost around one hundred dollars per foot of line; it must become more economical. Seaside settlements can dump their waste material into the water or onto the sea ice, but those inland have to burn it. Sumping into the ground is impossible; for even in the heat of summer the ground is frozen solid from, at most, six inches below the surface. Incomplete incineration is a problem now because there is no good, inexpensive burning device; what then happens when infected material is left in the cold? Preliminary studies on bacterial, viral, and amebic pathogens have been done under controlled laboratory conditions, but much more work is needed before the public health officer can approve or disapprove of any mode of sewage treatment.

Another problem is brought forward from these considerations, namely, how does cold affect pathogenicity? Will harmful organisms become tame and vice versa after exposure to the polar environment?

As limitless as the problems of applied medicine are those in the realm of pure medical science. Let us consider a few of these. Increasingly are we becoming aware of diurnal cycles of endocrine secretion and other internal activities; how

are these affected under conditions of total daylight and total darkness? Without day and night we are left without our usual time cues; can man function in timelessness, or does his confusion render him helpless and ineffective? The expanse of the icecap provides an excellent milieu for the study of sound localization and other phenomena that depend somewhat on orientation in space. Something else interesting to study is how the northland natives have learned to avoid the deficiency diseases we Americans and Europeans are prone to develop from living off the land. How have they learned to eat preferentially those plants and viscera (and even the stomach contents of ruminants) that, unpalatable to our tastes, are richest in the water-soluble vitamins?[4]

At this point the question might reasonably be asked, "Sure, the Arctic has tremendous possibilities, but isn't it awfully dangerous living there?" Most of the accounts of life within the Arctic or Antarctic Circles, even today, imply or are explicit concerning great danger with every minute's existence; the inference is that anyone and everyone who works there is an intrepid adventurer or a man so dedicated to his work that not even the horrible environment can deter him from it.

Nonsense! The men and women working there are no different from us; we have our jobs in Middletown, U. S. A., or France or Australia; they have theirs in the north. Just as we have learned that it is safer to cross an intersection when the light is green, they have their "homely" safety precepts. The "Arctic Expert" would call these "common sense," but, since this commodity is apparent often only after explanation, here are some, briefly: To leave the community, even as short a distance as a quarter mile, one must be prepared for sudden isolation by storm. Therefore, at all times one has with him enough food, fuel, and clothing for at least several days; if isolated, stay put, keep warm, keep fed, and above all keep busy. One more item of "common sense" is not to take needless chances—after all, we would not try to drive our highways blindfolded despite the cocksure phrase, "I know this road so well that. . . ."

The adherence to these precepts does not require full-time, conscious thinking; they become second nature. So life in the North (or South) is most emphatically not a struggle for existence. Fruitful, meaningful, important work has been done, is being done, and will be done.

There is some germ of the pioneer spirit in most of us yet. Here is probably the last geographic frontier (on this sphere, anyway). Someone will take advantage of it; we will have to know about it.

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Addendum

May the reader with interest beyond this article be referred to the extremely entertaining chapter on the Arctic in (of all places!) the "Encyclopædia Britannica," 1951. Its distilled recounting of the later scientific explorations and Arctic ecology reads as well as novels.

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Cryptococcosis

Further Observations and Experiences with Amphotericin B

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Infections due to Cryptococcus neoformans (Torula histolytica) continue to create diagnostic and therapeutic problems. Since our previously reported experience with this type of infection,[1] we have studied eight additional patients with cryptococcosis. Five of these patients have had meningoencephalitis and have been treated with the antibiotic, amphotericin B. Detailed reports of the diagnostic difficulties encountered in these five patients and their response to therapy with amphotericin B seem indicated.

Submitted for publication Nov. 25, 1958.

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Report of Cases

CASE 1.—A 43-year-old industrialist first came to the Mayo Clinic in July, 1955, complaining of episodic semiconsciousness and occipital headache of seven months' duration. In April, 1955, he had been hospitalized elsewhere, and culture of his spinal fluid had yielded C. neoformans.

Physical findings at the clinic were within normal limits except for marked obesity. Laboratory data on this and subsequent visits included results of urinalyses and estimations of the concentration of hemoglobin, the number of erythrocytes and leukocytes, and the sedimentation rate of erythrocytes, together with roentgenograms of the head and chest, and the Kline test, as indicated. Results were negative or within normal limits. Results of examination of the spinal fluid are given in Table 1, and cultures were positive for C. neoformans.

When the patient returned one month later for treatment, he stated that his headaches had continued, and again he described lapsing into a state

TABLE 1.—*Results of Analysis of Spinal Fluid in Case 1*

Date	Lymphocytes/ Cu. Mm.	Polys/ Cu. Mm.*	Protein, Mg/100 Ml.	Sugar, Mg/100 Ml.	Chlorides, Mg./100 Ml.	Culture †
1955						
July 25	57	158	200	35	726	+
Sept. 9	220	2	250	56	693	+
14	142	41	120	72	693	+
16	144	28	180	74	653	+
19	30	10	160	66	693	—
1956						
Jan. 19	85	55	160	50	726	+
July 18	229	61	300	65	714	+
Sept. 14	58	112	200	56	770	+
1957						
Feb. 7	147	256	240	35	601	+
March 26	120	138	200	28	693	+
April 6	93	8				—
12	101	7	300			—
26	4		180			—
May 8	4		200			—
July 24						—
Oct. 2						—
1958						
Jan. 3						—
Aug. 8						—

* Polymorphonuclear leukocytes.

† + indicates positive; —, negative.

of semicoma at times, which would persist for several hours during which he was aroused only with difficulty. Physical findings were essentially unchanged. Again cultures of the spinal fluid grew C. neoformans.

Because in vitro inhibition tests had indicated that the cryptococci were sensitive to the action of polymyxin B (Aerosporin), the patient was given 50 mg. of this agent every eight hours by intramuscular injection, from Aug. 26 through Sept. 1, and 50 mg. every six hours, from Sept. 2 through 23. During this period complaints were heard of acroparesthesia and soreness at the sites of injection of the polymyxin B. Also during this treatment, 0.5 mg. of polymyxin B was given intrathecally on six occasions. After cessation of treatment, the patient was subjectively much improved and the number of cells in the cerebrospinal fluid appeared to have been decreased (Table 1).

The patient returned in January, 1956. He had felt generally well, no longer had headaches, and had had only one episode of semiconsciousness. Results of physical examination and the routine laboratory data were essentially normal, as before, except for the obesity. An electroencephalogram revealed dysrhythmia, Grade 1, which, while generalized, was maximal in the left Sylvian area. Cultures of the spinal fluid ultimately grew out C. neoformans (Table 1).

On his return six months later, in July, 1956, the patient's only complaint was an occasional headache, relieved by salicylates. Again results of physical and the previously mentioned laboratory examinations were within normal limits except for the obesity.

Because data accumulated in the laboratory indicated that the sensitivity of the cryptococci to various antifungal agents changed with changes in temperature, a trial of treatment which would include hyperthermia was undertaken. Since laboratory data also had indicated that cryptococci isolated from the patient's spinal fluid were sensitive to sulfonamides as well as to polymyxin B, these agents were incorporated in the treatment program.

The patient's oral temperature was elevated to the vicinity of 103 F for approximately two hours each day for 17 days. Polymyxin B, in amounts of 50 mg., was given every eight hours by the intramuscular route with hyperthermia in order to see whether the combined treatment might be more effective than polymyxin B alone. After eight days an urticarial reaction developed, apparently due to the polymyxin B. Thereafter the patient was treated by hyperthermia and 1 gm. of sulfadiazine by the oral route every six hours for seven days. Cultures of the spinal fluid remained positive for C. neoformans.

In February, 1957, the patient returned again. He had felt well except for the occipital headaches and the spells of semiconsciousness. Again results of physical examination and the previously mentioned laboratory tests were within normal limits except for continued obesity. The patient was dismissed to return in a month for treatment with amphotericin B.

TABLE 2.—*Concentration* of Amphotericin B in Serum and Spinal Fluid During Intravenous Administration in Case 1*

Date		Dose, Mg.	Concentration, Units/Ml.	Fluid Examined
1957				
March	27	4,000 †	0	Blood
	28	25 ‡	0	Blood
	29	25	0	Blood
April	2	25	0.95	Blood
	4	50	1.27	Blood
		50	1.14	Blood
	5	50	1.14	Blood
		50	0.95	Blood
	6	75	1.8	Blood
		75	1.52	Blood
			0	Spinal
		75	1.8	Blood
	8	75	0	Spinal

* Approximately 4 hours after intravenous administration was begun each day.

† Oral.

‡ Intravenous on this and subsequent days.

On the return visit, in March, 1957, the patient received 4 gm. of amphotericin B by mouth daily for several days, but amphotericin B could not be demonstrated in the blood (Table 2).

Therefore, the patient was given 25 mg. of amphotericin B in 1,000 ml. of 5% dextrose in distilled water by the intravenous route daily. The infusion was allowed to run in over a period of eight hours. After five days, when it was apparent that the patient was tolerating the medication well, the dose was increased to 50 mg. daily. A chill developed but was successfully counteracted by decreasing the rate of infusion. Three days later the daily dose was increased to 75 mg., and this was tolerated without untoward reaction. After approximately 10 days the daily dose was increased to 100 mg. This change coincided with an increase in the concentration of urea in the blood, and hence the dose was reduced to 75 mg. daily. From the date that 50 mg. of amphotericin B was first given, the patient was treated for 38 days; the approximate amount of the agent received was 2.5 gm. The concentration of urea in the blood remained within normal limits after reduction of the dose to 75 mg. a day. Liver function, as determined by the sulfobromophthalein (Bromsulphalein) test, urine, concentration of hemoglobin, number of leukocytes, and differential counts remained normal during treatment.

Amphotericin B was detectable in the serum from the time that 50 mg. of amphotericin B daily was

administered (Table 2). On April 6, four days after the 50 mg. doses of amphotericin B were begun, cultures of the spinal fluid were negative for C. neoformans. Several subsequent cultures of spinal fluid, including the most recent one, in August, 1958, have been negative for cryptococci. A reply to a letter of inquiry, written in November, 1958, revealed that the patient had continued to remain well.

Comment.—Although not curative, polymyxin appeared to have some effect on the Cryptococcus, since headaches disappeared, the narcoleptoid episodes were decreased in incidence, and results of analysis of spinal fluid approached normal temporarily. The beneficial effects of amphotericin B seem definite in this case. The absence of detectable levels of amphotericin B in the patient's spinal fluid during intravenous administration of the agent, with apparent arrest of the meningeal disease, might be considered as militating against the need for intrathecal administration of the antibiotic in other victims of the disease.

CASE 2.—A 63-year-old man first presented himself at the clinic March 4, 1957, complaining of occipital headaches of two months' duration. Loss of 10 lb., vomiting, and a temperature which had reached as high as 103 F had occurred. A tremor of the right hand, present for some 30 years, had become more pronounced. For the previous week he had found it necessary to use a cane on walking.

The initial physical examination at the clinic revealed blood pressure of 160 mm. of mercury systolic and 100 mm. diastolic, sonorous and sibilant rales over the right side of the chest, a tremor of the right upper extremity of the so-called pill-rolling variety which was worse with intention, clonus of the right lower extremity, hyperactive deep reflexes on the right, vertical nystagmus on lateral gaze, and some slurring of the speech.

Routine laboratory data, including results of urinalysis and tests on the blood, were negative or within normal limits. Roentgenograms of the chest revealed a mass in the right hilus, with associated collapse of the right middle lobe. Roentgenograms of the head were read as negative. Cultures of the spinal fluid were positive for C. neoformans (Table 3).

Bronchoscopy revealed hard thickened tissues on the medial wall of the bronchus intermedius, the middle lobe bronchus, and immediately below the orifice of the superior division of the right lower lobe. Several specimens of tissue taken from these areas revealed granulomatous inflammatory tissue, cultures of which, however, were reported as negative for C. neoformans.

Pneumoencephalography revealed good filling of the ventricular system without evidence of a space-occupying lesion. An electroencephalographic tracing was normal. Electromyography revealed no definite evidence of denervation. The patient continued to run a fever intermittently, with a temperature which at its height reached 102 F. For one week he was given 4 gm. of amphotericin B by mouth each day, but at no time was any of the agent detected in the blood. We initiated therapy with amphotericin B, by the intravenous route, in amounts of 25 mg. each day, delivered over an eight-hour period. After the initial intravenous injection of the agent, the patient had a chill. Consequently, administration of the same amount each day was continued, but more time was consumed in delivering it. Seven days after intravenous use of the agent began the dose was

TABLE 3.—*Results of Analysis of Spinal Fluid in Case 2*

Date		Lymphocytes/ Cu. Mm.	Polys/ Cu. Mm.*	Protein, Mg/100 Ml.	Sugar, Mg/100 Ml.	Chlorides, Mg./100 Ml.	Culture †
1957							
March	12	14	20	200	13	649	+
	29	14	3		15	620	+
April	12	14	3	300			+
	20	40	24	300			+
	23	0	16	300			+
	25	6	21	200			—
	27	1	4	400			—
May	1	0	0	350			—
	4	12	4	65	35	680	+
	8	12	8	400			—
June	24	6	0	400	48	693	—
	27	2	1	400			—
1958							
Aug.	16						—

* Polymorphonuclear leukocytes.
† + indicates positive; —, negative.

increased to 50 mg. per day and was delivered over a period of 10 hours; a chill began approximately one and one-half hours after the infusion was instituted. On the fourth day that he was given 50 mg., chills during the infusion ceased, and therefore the dose was increased to 75 mg. per day.

On April 11, because of the persistently positive cultures of the spinal fluid, the dose of amphotericin B was increased to 100 mg. daily, and this regimen was continued through May 4. On April 17 and 20, he was given 0.75 mg. of the agent intrathecally, and from April 23 to May 4, he was given 1 mg. intrathecally each day.

At the conclusion of treatment, on May 4, the patient had been afebrile for approximately 72 hours; he was speaking well, was alert, and no longer had headaches. He had received approximately 3.25 gm. of amphotericin B intravenously in 40 days.

As is apparent in Table 3, cultures of the spinal fluid continued to be positive for cryptococci through April 23. The ones obtained on April 25 and 27 and May 1 and 8 were reported as negative. However, one taken on May 4 had been reported as positive.

The patient returned to the clinic on June 24, 1957, and was asymptomatic except for the evidences of hemi-Parkinsonism. He had regained his strength, could walk without a cane, and felt about as well as he had prior to the onset of the cryptococcal infection. Cultures of the spinal fluid were negative for C. neoformans. Replies to letters of inquiry written in December, 1957, and March and November, 1958, established that the patient had continued to remain well, except for anosmia. Cultures of the spinal fluid for cryptococcosis, performed elsewhere in August, 1958, were reported as negative.

Comment.—The persistently positive cultures of the patient's spinal fluid despite daily intravenous administration of amphotericin B in amounts of 100 mg. prompted the decision to give the agent simultaneously by the intrathecal route. The positive culture of the spinal fluid, obtained near the termination of therapy, caused us some uneasiness, but the patient's subsequent course and negative cultures have been reassuring.

CASE 3.—The patient was first examined at the clinic in 1954, at which time she was 21 years old. She related that one and one-half years previously, during her second pregnancy, biopsy of nodes in the right cervical region had revealed Hodgkin's disease, and roentgen therapy had caused regression of the involved nodes. Later, nodes in the left side of the neck and the spleen had become enlarged but regressed after roentgen therapy. In 1954, anorexia, fatigue, and loss of weight caused her to come to the clinic.

Physical examination at the clinic revealed slightly enlarged, firm, nontender nodes in the left supraclavicular area. Laboratory data were within normal limits except for roentgenograms of the chest, which showed infiltration in the midlung fields bilaterally. Slides of the nodes removed elsewhere were reviewed, and the findings were consistent with the diagnosis of Hodgkin's disease. Treatment with 20 mg. of mechlorethamine hydrochloride (nitrogen mustard) in one intravenous injection was advised.

The patient returned July 18, 1957. Three weeks previously she had begun to lose weight and complained of general malaise. She had had difficulties with her vision for two weeks and trouble with swallowing and speech for 1 week. Four days before admission, she began to vomit and became mentally confused.

The patient was poorly nourished, semicomatose and could barely see. Examination revealed bilateral complete sixth nerve palsy, bilateral orbicularis palsy (more marked on the right), depressed corneal reflexes, and bilateral acutely choked disks (3 D. on the right and 4 D. on the left). Marked nuchal rigidity, weakness of the right side of the face with inability to move the right forehead, and moderate to severe weakness of the 6th, 7th, 10th, and 11th cranial nerves were evident. Both eighth nerves also were considerably affected. The spleen was palpable 2 in. below the left costal margin. The temperature was 99 F (rectally).

Results of the usual laboratory tests on the blood and urine were negative or within normal limits. Roentgenograms of the chest revealed infiltration in the midlung fields bilaterally. Examination of the cerebrospinal fluid revealed budding yeast-like organisms, and cultures were reported subsequently as showing C. neoformans (Table 4).

Because of the increased intracranial pressure, left ventriculostomy and ventriculography were performed. Clear ventricular fluid under pressure escaped, and a total of about 25 cc. of ventricular fluid was fractionally removed from each ventricle. Air passed from left to right and in the opposite direction. A rubber catheter was placed in the left lateral ventricle for intermittent drainage. The ventriculograms revealed dilatation of both lateral ventricles, no air in the aqueduct and fourth ventricle, but some air in the third ventricle, although the anterior portion was not too well filled. The ventricular fluid also contained C. neoformans on both smear and culture.

On July 22, amphotericin B, 25 mg., was administered intravenously in eight hours. Since the patient tolerated the procedure well, the dose was increased on the following day to 50 mg. and was continued at this level for the next two weeks.

TABLE 4.—*Results of Analysis of Cerebrospinal Fluid in Case 3*

Date	Source *	Lymphocytes/ Cu. Mm.	Polys/ Cu. Mm.†	Protein, Mg/100 Ml.	Sugar, Mg/100 Ml.	Chlorides, Mg./100 Ml.	Smear ‡	Culture ‡
1957								
July 19	S	88	5	75	60	578	+	+
	V(R)	24		100			+	+
	V(L)	103	34	200			+	+
26	S	5	21	400	30	627	+	+
30	S	21	336					
Aug. 2	S	20	3	400	38	594	+	+
13	S	16	27	100	58	714	−	+
14	S	14	30				−	−
16	V	6	133	130	53	644	+	+§
	S	6	30		43	621	−	−
Oct. 15	S	12		120-150	Normal	Normal		+
1958								
March 15							−	−
Aug. 4	S	23	9	75	43	693	+	+
7	S	16	5	60	43	710	+	+
Sept. 9	S	1	0	50	56	693	+	+
18	S	7	22	100			+	+
22	S						+	+
23	S						+	+

* S indicates spinal fluid; V(R), right ventricular fluid; V(L), left ventricular fluid.
† Polymorphonuclear leukocytes.
‡ + indicates positive; −, negative.
§ Single colony in 1 tube, 2 days after treatment was stopped.

Tube feedings were maintained; the clamp on the ventricular tube was opened and fluid allowed to drain; this drainage was regulated by keeping the drainage bottle at a level of approximately 1 in. above the forehead of the supine patient. The pressure in the ventricle was kept at about 4 cm. of cerebrospinal fluid. Intermittent occlusion of the ventriculostomy tube appeared to be associated with increased restlessness on the part of the patient, or, if the ventriculostomy tube failed to drain well, the patient would lapse into coma and blood pressure would be elevated.

On July 24, two days after intravenous therapy with amphotericin B was initiated, it was decided to give 0.5 mg. of the agent intrathecally and also intraventricularly, each on alternate days. Amphotericin B was given intravenously in amounts of 50 mg. through Aug. 4, and during this time, the C. neoformans persisted in cultures of the spinal fluid and ventricular fluid. Until Aug. 1, no amphotericin had been detected in the blood, but on that date 1.19μg. of amphotericin per milliliter was present as well as 0.53μg. per milliliter in the spinal fluid (Table 5).

Because of the failure to eliminate the cryptococci, the daily intravenous dose of amphotericin B was increased to 75 mg. on Aug. 5, and was continued through Aug. 31. On Aug. 12, for the first time cultures of the spinal fluid were negative for cryptococci but cultures of the ventricular fluid remained positive. On Aug. 14, cultures of the spinal fluid and on Aug. 16, cultures of the ventricular fluid were negative for cryptococci (Table 4).

On Aug. 17, the patient became much more alert, began to talk freely, and was oriented and able

TABLE 5.—*Concentration of Amphotericin B in Blood Serum and Spinal and Ventricular Fluids During Intravenous Administration in Case 3*

Date	Dose,* Mg.	Concentration Determined: Hr. After Beginning I. V. Dose	Concentration Determined: μg/Ml.	Fluid Examined
1957				
July 25	50	4	0	Blood
			0	Spinal fluid
27	50	4	0	Spinal fluid
30	50	5	0	Spinal fluid
Aug. 1	50	3	1.19	Blood
			0.53	Spinal fluid
2	50	4	0.53	Spinal fluid
3	50	6	0	Spinal fluid
			0	Ventricular fluid
5	75	6	0.5	Spinal fluid
6	75	4	2.25	Blood
			0.5	Ventricular fluid
1958				
Sept. 10	75	4	2.25	Blood
			0	Spinal fluid

* One dose, given intravenously in 8 to 12 hours daily; from July 24, 1957, through Aug. 19, 1957, dose of 0.5 mg. was given intrathecally and intraventricularly on alternate days.

to cooperate well. Examination on Aug. 19, revealed virtual blindness in the right eye, but the patient could count fingers with the left eye. The nerve head in the right eye was flat, but that in the left eye was elevated 2 D. On Aug. 26, the papilledema had almost disappeared; the right optic disk was flat, and the left disk was elevated less than 1 D. The patient began to feed herself and was able to walk to the bathroom with help. On Aug. 31, the optic nerve heads were flat and the patient could count fingers with both eyes. On Aug. 31, administration of amphotericin was discontinued and the tube was removed from the ventricle. The patient had received 2.75 gm. of amphotericin B by the intravenous route in 42 days. On Sept. 4, the patient was dismissed.

The cultures of the spinal and ventricular fluids, obtained on Aug. 16, included one culture of ventricular fluid which after prolonged observation grew out a single colony of cryptococci. Because the patient was relatively well clinically, further therapy was postponed.

Cultures of a sample of the patient's spinal fluid sent to us in late September, 1957, grew out C. neoformans, and further therapy seemed indicated. The patient returned Oct. 15, 1957, and further cultures of the spinal fluid revealed the fungus (Table 4).

Amphotericin B again was given intravenously in gradually increasing increments starting with 25 mg. daily. After 75 mg. had been given daily for 15 days, treatment was halted for 2 days because the value for urea had risen from 22 to 88 mg. per 100 ml. of blood. Thereafter, 50 mg. of amphotericin B was given daily for three days, and, since the value for urea remained normal, the dose was increased to 75 mg. for an additional eight days. The patient had received a total of 1.8 gm. of amphotericin B in about 30 days. Cultures of the spinal fluid were negative at the time of dismissal from the hospital and also in March, 1958.

From November, 1957, the patient considered herself well; she partook in such activities as horseback riding and water skiing, along with caring for her home and children unaided. At that time too she recognized no handicap except the decreased vision. In mid-July, 1958, she noted some decrease in her energy and a feeling of vague malaise. On Aug. 3, she had a sudden occipital headache on arising in the morning and began to vomit, and fever (temperature of 103 F) developed.

On readmission to the clinic, on Aug. 4, the patient's general status appeared to be comparatively good except for mild languor. She was afebrile, had ceased vomiting, and, except for homonymous hemianopsia, loss of the sensation of smell, slight right facial weakness, and questionable weakness of the muscles of the legs, all of which appeared to represent residua of her previous difficulties, physical examination was not revealing. Both smears and cultures of the spinal fluid revealed C. neoformans. Other laboratory data on blood and urine were within normal limits. Roentgenograms of the chest revealed no substantial change.

Amphotericin B, 25 mg., was given intravenously each day for one week; then 37.5 mg. was given daily for four days and 50 mg. for one week. On the fourth day after she had received 75 mg. of amphotericin B, it was necessary to stop treatment because of azotemia. Thereafter 75 mg. of the agent was given intermittently for an additional eight days; the intermittency was dictated by recurring azotemia. During this period 0.5 mg. of amphotericin B was given intrathecally every second day for five doses. The patient had received a total of approximately 1.5 gm. of amphotericin B, and further therapy was not attempted (at the patient's request). It is apparent from Table 4 that smears and cultures of the spinal fluid continued to reveal C. neoformans.

Within one week after therapy with amphotericin B was started, the patient's headache had disappeared and she recovered her usual appetite and energy. However, in view of the continued presence of cryptococci in the spinal fluid, the outlook appears to be poor.

Comment.—Of the present series, this is the only patient who had detectable lymphoma. We and others, of course, have previously noted the concurrence of cryptococcosis and lymphoma. When treatment with amphotericin B was instituted, the patient's general status was poor, intracranial pressure was extremely high, and surgical drainage undoubtedly contributed much to her improvement. Unlike the previous patient, the positive culture of spinal fluid for C. neoformans, obtained near the termination of the initial period of treatment, proved significant but was not unexpected, in view of the patient's probably disturbed natural resistance dependent on the lymphoma and its therapy. This patient's course indicates that recurrences of cryptococcosis in patients with lymphoma and allied states are to be anticipated. This patient, like the previous one, had anosmia.

CASE 4.—A 58-year-old man was admitted to the clinic on June 8, 1957, with the chief complaint of frontal headache of four months' duration. He described the headache as being steady, progressively severer, and worsened by leaning forward

TABLE 6.—*Results of Analysis of Spinal Fluid in Case 4*

Date	Lymphocytes/ Cu. Mm.	Polys/ Cu. Mm.*	Protein, Mg./100 Ml.	Sugar, Mg/100 Ml.	Chlorides, Mg./100 Ml.	Smear †	Culture †
1957							
June 12	153	10	110	35	720	—	—
1958							
Feb. 19	240	25	140	19	734	—	—
March 3	193	19	180	24	710	—	+
April 10	226	6	180	19	726	—	—
24	124	2		37		—	—
May 2	113	8	120	53	683	—	—
9	85	0	120			—	—
13	128	2	80			—	—
June 9	17	1	50	63		—	—
23	15	0	45	51	733	—	—
30	11	1	40	60	726	—	—
Aug. 9						—	—
Nov. 7						—	—

* Polymorphonuclear leukocytes.
† + indicates positive; —, negative.

or jarring. He had been hospitalized elsewhere, and spinal taps showed several hundred leukocytes, the majority being lymphocytes. A pneumoencephalogram had been interpreted as showing "cortical atrophy."

Results of physical examination at the clinic, including examination of the central nervous system, were within normal limits except for slight bilateral nerve deafness.

Laboratory data on blood and urine, results of the Kline test, and roentgenograms of the head and thorax were negative or within normal limits. Spinal puncture revealed an increased number of cells, which were predominantly lymphocytes, and an elevated value for protein (Table 6). Cultures of the spinal fluid were reported negative for cryptococci after an interval of six weeks.

The patient returned to the clinic Feb. 18, 1958. His headache had continued, and again the spinal fluid contained an increased number of cells, with a predominance of lymphocytes and an increase in the protein content.

An electroencephalogram showed dysrhythmia over the right frontal region which, when it was compared with a recording made in June, 1957, suggested increased abnormality. Cultures of the spinal fluid, collected on March 3, subsequently grew C. neoformans.

On April 12, amphotericin B, 25 mg., was given intravenously in six hours; on the following day, 50 mg. was given; on the third day, 75 mg., and for the next two days, 100 mg. daily. The blood urea, which had measured 24 mg. per 100 ml. prior to treatment, at the end of the fifth day of treatment measured 92 mg. Treatment, therefore, was halted for six days.

The patient then was given 50 mg. of the agent daily in 6 to 10 hours for 11 days, when recurrence of azotemia was the basis for stopping treatment. After an interval of three days, 50 mg. of the agent was given intravenously on alternate days for six doses, and, since the value for urea remained normal, 50 mg. of the agent was given daily, beginning May 25, for 20 days, when azotemia recurred. After treatment was interrupted for five days, the urea was within normal limits and 50 mg. of amphotericin B was given intravenously each day for another week.

The number of cells and the values for protein in the cerebrospinal fluid progressively decreased to normal limits during therapy (Table 6). Also no cultures of the spinal fluid were positive for cryptococci after treatment was initiated.

The urine and blood and liver function, as indicated by the usual tests, remained within normal limits during treatment.

The patient received a total of 3.25 gm. of amphotericin B by the intravenous route in 49 treatment days; however, 76 days in all were consumed because of the periodic discontinuation of therapy dictated by the azotemic reactions. Inquiry in November, 1958, established that the patient had remained well.

Comment.—The patient's course exemplifies the need for continued suspicion of cryptococcosis as the etiologic agent in cases of chronic meningoencephalitis, since one or more negative cultures of spinal fluid cannot exclude the disease. Although Cases 1 to 3 also demonstrate the azotemic propensities of amphotericin B, the reaction in Case 4 was more striking. Although the actual number of treatment days in this case approximates that in the preceding cases, almost twice as many days of hospitalization

were required because of the azotemic reactions and consequent interruption of the regimen.

CASE 5.—A 50-year-old white farmer from Canada was admitted to the clinic April 10, 1958. His previous visits to the clinic were in 1949 and 1954, at which times he had chronic otitis media on the right, and in 1953, when leukoplakia was excised from his lower lip. Laboratory data, accumulated in 1949, 1953, and 1954, were within normal limits except that roentgenograms of the mastoid regions revealed bilateral sclerosis and a few remaining cells in the left mastoid.

The patient's chief complaint in April, 1958, was of persistent headache of five weeks' duration, which had occurred after a paroxysm of coughing. In October, 1957, a common cold (or so he thought) was manifested by a cough productive of mucus associated with chilly sensations, and, since his symptoms persisted, he was hospitalized in December, 1957, for two weeks. Roentgenograms of the chest had been negative at that time.

In March, 1958, chills and a fever (temperature of 102 F, orally) had caused hospitalization for nine days. At that time the frontal headache, which was his chief reason for visiting the clinic, developed. Movements of his head, sneezing, and straining at defecation aggravated the complaint.

Physical examination revealed blurring of the margins of the optic disks, absence of venous pulses in the disks, engorgement of the retinal veins, and elevation of the disks of less than 1 D. The chronic otitis media on the right was noted again. No focal neurologic findings were detected.

Laboratory data from tests of urine and blood used routinely in these cases, the Kline test, cultures of the blood, and roentgenograms of the head and chest were negative or within normal limits. Roentgenograms of the mastoids revealed the bilateral sclerosis. Reexamination of the optic fundi after an interval of three days revealed definite striations in the retina above and below the disk on the right, a small deep choroidal hemorrhage at the nasal margin of the right disk, and overlying it a more punctate hemorrhage. Inferonasally to the disk the capillaries appeared dilated, and early papilledema was diagnosed.

The patient was hospitalized for further observation, and three days thereafter the optic disks were elevated approximately 2 D. on the right and 1.5 D. on the left, with blurring of all the margins and moderate venous engorgement. Hemorrhage was noted in two areas to the left of the right disk and in one area to the right of the left disk. Electroencephalograms revealed a dysrhythmia, Grade 2, which was generalized but maximal over the right fronto-Sylvian area, with some nonspecific slowing, maximal in the posterior occipital region. Bilateral percutaneous carotid angiography and combined ventriculography and pneumoencephalography did not reveal evidence of a space-occupying lesion.

General and neurologic examinations continued to disclose no abnormalities except for questionable stiffness of the neck. The oral temperature vacillated from normal to 102 F.

On April 30, isolation of C. neoformans from the cerebrospinal fluid was reported (Table 7) and treatment with amphotericin B was begun with an initial dose of 25 mg. During intravenous administration, when approximately 6 mg. of the agent had been given, the patient had a shaking chill and vomited copiously. The next day, one hour after the intravenous administration was begun, the patient again had chills, became restless, appeared to be confused, and had a temperature of 104 F. The same sequence of events continued daily, necessitating discontinuation of the intravenous medication when less than 0.5 liter had been delivered. On the fifth day of treatment the patient tolerated 800 ml. of the intravenous solution before administration had to be discontinued because of chills, restlessness, confusion, and fever. On the eighth day, the patient tolerated the full dose of the agent. Therefore on the ninth day, 50 mg. was given and tolerated well, but on the following day, when a dose of 75 mg. was being administered, chills and fever (temperature to 102 F) developed.

TABLE 7.—*Results of Analysis of Spinal Fluid in Case 5*

Date	Lymphocytes/ Cu. Mm.	Polys/ Cu. Mm.*	Protein, Mg/100 Ml.	Sugar, Mg/100 Ml.	Chlorides, Mg./100 Ml.	Smear †	Culture †
1958							
April 28	113	55	100	43	651	+	+
May 15	240	3	75			+	+
June 9	114		40	48	706	—	—
23	27		35	66	726	—	—
July 7	39		45	63	706	—	—
31	27		30			—	—
Oct. 24	1	10	65	35	648	+	+

* Polymorphonuclear leukocytes.
† + indicates positive; —, negative.

The patient was given acetylsalicylic acid in an attempt to control the untoward reactions, after which he tolerated 75 mg. of amphotericin B daily without difficulty for three days. Therefore, 100 mg. was given, but after two days of this dose, the value for blood urea, which previously had been normal, was found to be 78 mg. Medication was discontinued for five days until the azotemia abated. The patient, during that interval, was given 0.5 mg. of amphotericin B intrathecally each day, and this resulted in severe headaches.

The amphotericin B again was given intravenously in a dose of 50 mg. daily for two weeks without difficulty. The patient improved clinically, and the optic fundi appeared essentially normal. The medication was continued in doses of 50 mg. daily for another two weeks, at which time chills recurred and acetylsalicylic acid was given again. Because the acetylsalicylic acid brought about dyspepsia, it was replaced by an antihistaminic.

On the 37th treatment day, after he had received 50 mg. of amphotericin daily, the value for urea in the blood was 80 mg. and the administration of amphotericin was discontinued.

Several attempts to reinstitute therapy with amphotericin were stopped by chills and fever from as little as 20 mg. of the agent. The patient had received approximately 3.4 gm. of amphotericin B intravenously. Of 65 days consumed in the giving of this amount of the agent, 12 were those during which azotemia or other untoward reaction prevented administration of the antibiotic. As is apparent from Table 7, after May 15, smears and cultures of the spinal fluid were negative for C. neoformans, and gradually the values for cells and protein content in the fluid approached normal.

Approximately three and one-half months after this patient's dismissal from the clinic, frontal headaches and recurrent fever (temperature to 103 F orally) again developed. Again early papilledema was noted, and smears and cultures of the spinal fluid revealed C. neoformans. Because of the patient's previous untoward reactions to amphotericin B, it was administered initially in amounts of 12.5 mg. by the intravenous route over a period of 10 to 12 hours. This dose was increased in increments of 12.5 mg. at intervals of three days, and currently he is accepting 50 mg. daily without untoward effect. At the time of this writing he is asymptomatic and his papilledema has receded.*

Comment.—We have failed to detect why this patient had a relapse. Since the patient described in Case 3 had lymphoma and also suffered a relapse, we have attempted to demonstrate such a lesion in this patient, but without result.

* C. neoformans persisted in the spinal fluid despite continued treatment with amphotericin B for more than one month. This case is classed as a treatment failure.

Comment

Cryptococcosis is caused by a yeast-like fungus, C. neoformans (T. histolytica). Infections caused by this organism are frequently manifested by meningoencephalitis, but lesions elsewhere in the body may precede lesions in the central nervous system and occasionally may predominate. The infection may be fulminating but is usually chronic and in occasional persons may be characterized by spontaneous remissions, sometimes of prolonged duration. It is this latter characteristic which may make evaluation of therapy difficult. Although apparent cures of localized pulmonary cryptococcosis by lobectomy have been reported by members of our group [1,2] and others,[3] treatment of cryptococcal meningoencephalitis has been disheartening until recently.

A review of cryptococcosis as a disease entity is not necessary, since this has been done previously. However, the advent of the antibiotic, amphotericin B, has made it desirable to discuss advances in the treatment of cryptococcal meningoencephalitis.

Amphotericin B was isolated from a species of Streptomyces. Other investigators [4-10] previously have presented data describing the antibiotic, its clinical use, and its application in fungal diseases, including cryptococcosis. Since only minimal absorption of amphotericin B follows oral administration, it usually is given parenterally for systemic infections.

At present, it is recommended that, when the agent is given intravenously, each milligram of the agent be dissolved in at least 5 ml. of 5% dextrose in distilled water. We have started treatment usually with an initial dose of approximately 0.25 mg. per kilogram of body weight, dissolved in the appropriate amount of diluent, and have delivered this intravenously in 6 to 12 hours. We have attempted to increase the dose gradually to approximately 1 mg. per kilogram of body weight daily, depending on the tolerance of the patient. It is recommended

that visible particles of the agent be filtered out of the solution before administration, and we place a filter used in transfusions of blood in the apparatus delivering the medication. Phlebitis at the site of administration, headaches, flushing, chills, fever, dyspepsia, and azotemia may result from the administration of amphotericin B. Diarrhea and respiratory distress are said to follow its use. Increasing the time taken to deliver the medication or decreasing or temporarily discontinuing the daily dose have been effective against side-effects in most of our patients.

Thus far, we have not recognized any ill effects of amphotericin B on the concentration of hemoglobin, number of erythrocytes or leukocytes, or liver function, and we have not detected evidence of irreversible damage to the kidneys. Rubin and Furcolow [10] mentioned one patient in whom the agent may have been hepatotoxic.

We agree with Appelbaum and Shtokalko [7] that the interval since termination of therapy in the cases described to date is inadequate to permit final approval of the drug. However, amphotericin B appears to be a promising anticryptococcal agent, even when one takes into consideration the natural tendency of the disease in an occasional patient to spontaneous remission of prolonged duration. Our preliminary conclusions on the application of amphotericin B are supported by the data supplied by Rubin and Furcolow.[10] These investigators presented 10 patients with cryptococcal meningitis, in 8 of whom the spinal fluids became free of fungi on repeated cultures. These eight patients were alive 2 to 24 months after discontinuation of therapy. Their patients had been given 50 to 100 mg. of amphotericin B daily or every other day by the intravenous route, for total dosages of 1.4 to 3.7 gm. Three of their eight paients had subsequent relapses. The two patients who died were moribund at the beginning of therapy, and little of the agent had been given before death supervened.

From our experience to date we can say that 50 to 100 mg. of amphotericin B, given daily, when possible, for a total of approximately six weeks, appears to have arrested cryptococcal meningoencephalitis in three patients. Relapses have occurred in two patients, one of whom has associated lymphomatous disease. The optimal dose of the agent is not established as yet, but in our experience it cannot exceed 100 mg. when administered daily by the intravenous route. The size of the dose and the likelihood of azotemia appear to be associated; thus patients of lower body weight will tolerate only smaller doses. How long to continue treatment in an individual case is not evident at this time, but the duration of treatment is probably dependent on the severity and duration of the infection. It also is not known whether intrathecal administration of the agent is necessary for cryptococcal meningitis. We gave the agent intrathecally to three of our five patients, however, because we have been unable to detect amphotericin B in cerebrospinal fluid aspirated from patients who have received it intravenously. On the other hand, one of our patients who did not receive the agent intrathecally and whose spinal fluid failed to show detectable amounts of amphotericin B apparently had clearance of the fungus from the central nervous system. Whether the agent actually must get into the cerebrospinal fluid in cases of meningoencephalitis is not known. Littman and associates [9] have successfully given the agent as an aerosol for inhalation therapy in amounts of 5 mg.

Amphotericin B apparently has afforded our patient with associated Hodgkin's disease several months of continued existence. It seems pertinent in this regard to stress again the not infrequent occurrence of cryptococcosis in victims of lymphomata and allied states. The apparent disturbance in natural resistance, which rendered this patient susceptible to superimposed cryptococcosis, also apparently militated against a more complete arrest of her fungal disease by amphotericin B. Approaching death in such patients may not necessarily be a function of the primary disease and, if found to be due to cryptococcosis, may be sub-

stantially delayed. A smear and culture for fungi should be made of the spinal fluid of persons with lymphomata and similar diseases with evidence of meningeal irritation.

The diagnosis of cryptococcosis is dependent on identification of the causative organism by direct examination and culture of tissue, pus, sputum, spinal fluid, or other body fluids. Occasionally, cryptococci can be seen when unstained spinal fluid is examined microscopically, but India-ink preparations of the spinal fluid are more likely to reveal the thick-walled and budding cells. In cases of cryptococcal meningitis, the number of cells in the cerebrospinal fluid is increased and lymphocytes almost always predominate. The concentration of protein in the cerebrospinal fluid usually exceeds 80 mg. per 100 ml., and the amount of sugar is usually less than 40 mg.

It should be pointed out also that one or more negative cultures of spinal fluid do not exclude the possibility of cryptococcal meningoencephalitis.

Summary

Infections due to Cryptococcus neoformans continue to create diagnostic and therapeutic problems. Eight patients with cryptococcal meningoencephalitis have been studied. Since our previously reported experience with cryptococcosis, amphotericin B has been made available for clinical use. In three of our five most recent patients, arrest of the disease appears to have been achieved by use of this antibiotic agent. The two patients who were similarly treated have had relapses of the disease; one of these patients also has Hodgkin's disease.

Mayo Clinic.

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Kanamycin

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Kanamycin was first described by Umezawa et al. in 1957 [1]; it is produced by Streptomyces kanamyceticus.

Chemistry

The crystalline sulfate of kanamycin is water-soluble, alcohol-insoluble, and basic. It is a very stable compound with less than 10% loss after autoclaving for one hour at 120 C; it is stable over a pH range of 2 to 11. Cron and his co-workers [2] have determined that kanamycin consists of two amino sugars linked glycosidally to 2-deoxystreptamine, with the structural formula shown in Figure 1. This structure resembles that of neomycin and has some similarity to streptomycin.

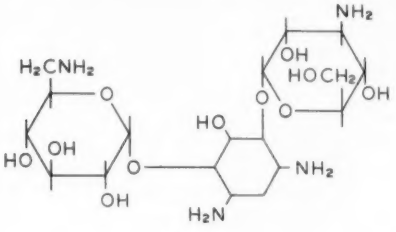

Figure 1

Paper chromatography of kanamycin preparations reveals a second antibiotic, kanamycin B. Kanamycin B exhibited more toxicity than kanamycin A in animal studies [3] and is present to the extent of only 2% to 3% in later preparations of the drug.

Microbiological Studies

1. *Spectrum.*—In vitro, kanamycin is active against a variety of organisms (Gram-positive, Gram-negative, and acid-fast), as indicated in Table 1. In general, it is active against all Gram-negative organisms except Pseudomonas (relatively few strains are sensitive); it is only moderately active against Proteus but is still probably more active than any other single agent against this genus. It displays considerable activity also against Gram-positive organisms, but streptococci and pneumococci are moderately to highly resistant. Anaerobic organisms and fungi are highly resistant to kanamycin; because of this and the fact that this antibiotic has such a wide spectrum, kanamycin should prove useful in selective media for isolation of these organisms, just as neomycin has.[18] Preliminary data indicate that kanamycin is even less active against Bacteroides than neomycin and therefore may be more suitable in a selective medium for this genus.[8]

TABLE 1.—*In Vitro Kanamycin Sensitivity of Some Human Pathogens* *

Usually Sensitive	Sometimes Sensitive	Usually Resistant
Atypical AFB (photochromogens)	Alcaligenes †	Bacteroides
Aerobacter	D. pneumoniae	Candida species
B. anthracis	Proteus species	Clostridium species
Brucella	S. pyogenes	Coccidioides immitis
E. coli		Enterococci
Klebsiella		Other anaerobes
M. tuberculosis		Other fungi
Neisseria		Pseudomonas
Paracolons		Viridans Streptococcus
S. typhi		
Salmonella (other)		
Shigella		
Staphylococcus		
Vibrio †		

* This does not imply corresponding usefulness clinically (see Table 4) (data obtained from References 4-17).
† Very few strains tested.

Kanamycin sensitivity has been shown to vary according to a number of factors:

Submitted for publication Nov. 29, 1958.

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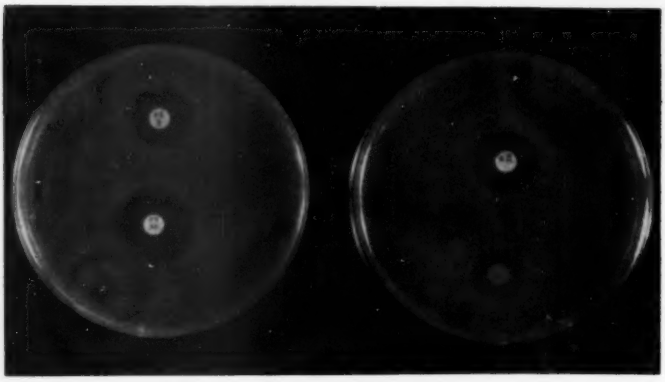

Fig. 2.—Disk sensitivity testing with kanamycin and neomycin. The test organism is a Staphylococcus which has "identical sensitivity" to kanamycin and to neomycin by tube- and plate-dilution tests. The larger zones about the kanamycin disks (*KX*) as compared to neomycin (*N*, and unlabeled) suggest greater diffusibility of kanamycin.

components of the culture medium, pH of the medium, size of inoculum, length of incubation of test, and type of test (tube-dilution, plate-dilution, or disk method).[8,19] Certain of these factors are more important with some organisms than with others. Results obtained by the technique proposed by Gourevitch et al.[19] are reproducible in widely separated laboratories and, in general, seem to tie in well with clinical results (taking into consideration achievable blood levels).

Comparative studies of disk sensitivity to kanamycin and neomycin, as correlated with tube-dilution and plate-dilution techniques, reveal that kanamycin regularly gives larger zones of inhibition than neomycin in spite of comparable sensitivity by the other methods (Fig. 2). This suggests that kanamycin diffuses more readily than neomycin.[8]

2. *Cross Resistance and Relative Susceptibility to Related Antibiotics.*—Virtually complete cross resistance is noted between kanamycin and the related antibiotics, neomycin and paromomycin. Induced resistance to streptomycin did not lead to resistance to the other three drugs, but organisms made resistant in vitro to these three were usually very resistant to streptomycin as well.[20] These relationships held true in organisms made resistant in vitro and in "naturally resistant" strains recovered from clinical material.[4,20] There is no cross resistance between kanamycin and antibiotics other than those mentioned above.

It appears that neomycin is slightly more active on a weight basis than kanamycin against certain organisms, particularly staphylococci[5,8,16,20]; conversely, kanamycin appears to be more active against Proteus than neomycin.[5,8] Obviously, such matters should be correlated with achievable blood levels and relative toxicity of both agents; unfortunately, good data on these points are not available in the case of neomycin.

3. *Mode of Action.*—Many investigators have noted that kanamycin is bactericidal at levels equal to or not much higher than cidal activity is rapid[4,9] and is more apparthose producing bacteriostasis. The bacterient against proliferating than against resting cells.[4]

4. *Development of Resistance.*—Resistance develops in vitro on repeated subculture in the presence of graded concentrations of kanamycin; the rate of development of resistance is relatively slow and compares to that observed with penicillin (rather than streptomycin).[4,9] Tubercle bacilli acquire kanamycin resistance rapidly.[4,6] Limited clinical experience suggests that development of resistance to kanamycin with clinical usage will not be a major problem, but development of resistance on therapy has been reported.[12]

Pharmacology

1. *Animal Studies.*—Acute and chronic toxicity studies and various other pharma-

cologic observations were made on different species of animals by Tisch et al.[21]

Acute toxicity studies in mice indicated somewhat less toxicity for kanamycin than for streptomycin under the same conditions. Intravenous injection in dogs in doses of less than 200 mg. per kilogram of body weight produced falls in blood pressure; doses of 250 mg. per kilogram produced respiratory paralysis.

Kanamycin was found to be less nephrotoxic than neomycin in dogs. In cats, streptomycin produced loss of vestibular function at smaller doses and in a shorter time than did kanamycin. A similar relationship held for dihydrostreptomycin and kanamycin with respect to auditory perception in rats.

In dogs, kanamycin was well absorbed after intramuscular and subcutaneous administration but was poorly absorbed after oral administration. After parenteral administration, the drug is excreted rapidly in the urine.

In anesthetized dogs, good concentrations of kanamycin appeared in the spinal fluid, but relatively small amounts were noted in the bile after intramuscular injection.

2. *In Humans.*—Pharmacologic data obtained in humans by a number of different investigators are in remarkable accord. Serum levels generally hit a peak one hour after intramuscular administration, level off or drop some at two hours, and then begin to drop relatively abruptly, and so levels are low at six to eight hours after injection and very low at 12 hours. There is no cumulative effect with repeated doses over long periods of time. Peak levels are generally 20μg. to 35μg. per milliliter of serum after intramuscular doses of 1 gm. (10 to 20 mg. per kilogram of body weight) and 5μg. to 15μg. per milliliter 6 hours after the dose; levels are often only 1-2μg. per milliliter or less at 12 hours.[5,7,8,12,14,15,22,23] Similar results have been obtained in children on comparable dosage.[13,24] Levels are lower with smaller doses, with average peak levels of 20μg. to 25μg. after 0.5 gm. doses and 10μg. to 15μg. after 0.25 gm. doses in adults. Doses should not be given less often than every 12 hours, in view of the low serum levels at that point; theoretically, at least, dosage every 6 to 8 hours would seem to be desirable, and Thurman and Platou[25] felt that they obtained better results clinically with this sort of a dosage regimen (as compared to dosage every 12 hours).

There is no evidence of serum binding of kanamycin.[5,26]

In the presence of impaired renal function (as measured by elevated creatinine levels) high serum concentrations have been observed (as high as 90μg. per milliliter at 5 hours after a dose of 1.5 gm. intramuscularly); high levels have also been noted in some elderly patients.[8]

Fifty to eighty per cent of intramuscularly administered kanamycin is excreted in the urine in the 24 hours after injection, most of it in the first 6 to 9 hours.[5,12] Urinary concentrations in the first six hours after intramuscular administration of the drug generally range from 200μg. to over 1,000μg. per milliliter after either single doses[5] or multiple doses.[12]

It appears that the major mechanism for renal excretion of kanamycin is glomerular filtration but that there is some tubular excretion as well.[26] Concurrent administration of probenecid does not enhance kanamycin serum levels.[27]

Table 2 presents data on diffusion of kanamycin into various body fluids of man

TABLE 2.—*Diffusion of Kanamycin in Man After Intramuscular Administration* *

Fluid or Tissue	Level, μg/Ml.	Concurrent Serum Level, μg/Ml.	Author
Spinal fluid	Trace	19.5-52.5	Boger & Gavin [17]
(meninges uninflamed)	<0.5-0.5	<0.5-16.0	Ruiz Sanchez et al. [24]
Saliva	<0.6	--	Boger & Gavin [17]
Bronchial secretions	0-10	13-112	Huang et al. [16]
Bile	<0.5-2.3	--	Finegold & Hewitt [20]
Feces	<50.0	--	Hewitt & Finegold [9]
Ascitic fluid	13.0	--	Hewitt & Finegold [9]
Pleural fluid	1.3-2.1	--	Finegold & Hewitt [20]
	5.5	5.2	White & Knight [12]

* Except for the spinal fluid, there have been very few observations; this is especially true for the last 4 materials.

TABLE 3.—*Oral Administration of Kanamycin*

	Dose, Gm/Day	Drug Level, μg/Ml.	Author
Serum levels	4	<0.4	Prigot et al.[31]
	6	<0.5	Cohn [32]
	6	<0.5-1.0	Finegold & Hewitt [36]
	8	<0.5-2.0	Ruiz Sanchez et al.[33]
	12	5.0 or less	Bunn et al.[7]
Fecal levels	6	4,400-10,000	Cohn [32]
	6	9,300-24,700	Hewitt & Finegold [9]
Urine levels	6	110.0	Finegold & Hewitt [36]
	8	0->256.0	Ruiz Sanchez et al.[33]

after intramuscular administration. Although there is apparently relatively good diffusion into pleural and ascitic fluids, biliary excretion is low, and relatively little kanamycin gets into the saliva or bronchial secretions or into the spinal fluid (in the presence of uninflamed meninges). The relatively low biliary excretion is confirmed by the low fecal level of drug and the lack of significant effect on the fecal microflora after intramuscular administration.[30]

Note in Table 3 that huge concentrations of kanamycin were attained in the feces after oral administration and that serum levels were extremely low. From 0.3% to 1.5% of the ingested dose appears in the urine.[31]

Toxicity in man will be considered as a separate item later in this paper.

Use in Experimental Infections

Kanamycin administered intramuscularly was effective in acute infections (intraperitoneal injection) in mice due to staphylococci, Proteus, and Klebsiella pneumoniae but was distinctly less active against pneumococcal and hemolytic streptococcal infections. Kanamycin was also effective in chronic staphylococcal infections in mice (produced by intravenous injection) both in terms of preventing death and by reduction in numbers of viable staphylococci in kidney tissue.[33]

Studies by Yanagisawa et al.[34] and Steenken and co-workers [6] demonstrate the effectiveness of kanamycin in experimental tuberculosis in guinea pigs; it was less active than isoniazid and slightly less so than streptomycin.

Clinical Use

1. *Oral Use.*—As indicated previously, when kanamycin is administered orally there is very little absorption. Hence, oral kanamycin therapy could only be expected to be useful through its activity against the normal intestinal microflora and certain intestinal pathogens.

The effectiveness of oral kanamycin (either in capsule form or as a syrup) in intestinal sterilization is well established. In our experience,[8,35] with 6 gm. of kanamycin base per day after a loading dose in eight patients on a standard hospital diet, kanamycin consistently eliminated all aerobic bacteria within 72 hours (and often within 24 to 36 hours) if a purgative was given with the first dose of drug to expedite passage through the gastrointestinal tract; in one case on prolonged therapy, highly resistant enterococci grew back in after two weeks. Bacteroides persisted in all patients (in large numbers in all except one case); the effect on other anaerobes was variable, but generally at least small numbers of lactobacilli persisted also. Candida often increased in numbers but did not reach the large numbers commonly seen with oral neomycin in smaller dosage (4 gm. of neomycin base activity daily). In one of our cases (Case Report [35]) a staphylococcal enterocolitis appeared 24 hours after treatment was discontinued (stool culture revealed no aerobes on the day treatment was stopped); apparently staphylococci grew back as the kanamycin was excreted and before the normal flora was restored.

Cohn [32] treated 18 patients for three days with 6 gm. of base activity of kanamycin daily after a loading dose and a laxative. His results were similar to ours except that streptococci persisted in 3 patients and Bacteroides were eliminated in 11 patients.

Faloon and Fisher [36] used doses of kanamycin varying from 3 to 12 gm. of base

activity daily in different patients. Two patients receiving 8 to 12 gm. daily had flora composed of Bacteroides, Clostridia, and yeasts while on therapy; one additional patient had only Bacteroides and Clostridia on this dosage. Two additional patients receiving 8 gm. of kanamycin daily had flora composed of coliforms and yeast in one case and lactobacilli only in the other.

Faloon and Fisher[36] also studied the effect of oral kanamycin therapy on blood ammonia levels and found considerable variation in these levels, although early results had been good. These authors felt that it was necessary to establish an optimal dose for the purpose of lowering ammonia production and that, until such a dose was established, neomycin would appear to be more reliable for this purpose. On the other hand, Chalmers et al.[37] felt that oral kanamycin (4 to 12 gm. of the sulfate daily, with an average of 8 gm.) had a beneficial effect on the cerebral manifestations of liver disease in 11 patients. Two patients with similar mental changes, EEG findings, and flapping tremor, on the basis of pulmonary, rather than hepatic, failure may also have been helped.

Several workers have used oral kanamycin (either alone or in conjunction with intramuscular therapy) for the treatment of various intestinal infections or carrier states. Ruiz Sánchez et al.[28] used kanamycin orally in 76 patients who were carriers of Entamoeba histolytica cysts; although there was a definite effect, results were inferior to those obtained in another group treated concurrently with oxytetracycline, in terms of rapidity of elimination of cysts, percentage of cases cleared, and percentage of patients cleared who were again positive on follow-up after treatment (in the latter case, reinfection rather than relapse is not excluded). These workers also treated three acute cases of amebic colitis; two had good responses to oral therapy, and the third, who was critically ill at the start of therapy, failed to respond to both oral and intramuscular kanamycin. One case of gastroenteritis, thought to be due to Escherichia coli, had a good response on oral kanamycin.[13] Two patients with Salmonella enteritis responded well to kanamycin orally.[38]

Thurman and Platou[39] used a combination of oral and intramuscular kanamycin in a variety of intestinal infections. Twelve cases of acute and 14 cases of chronic Shigella infection had good results. Six patients with acute Salmonella enteritis did well clinically, although one remained culturally positive, and five patients with chronic Salmonella infections appeared to have good results on the basis of preliminary observation. Two cases of typhoid fever were treated, with poor results. These authors, in a later publication,[25] indicate that, of 19 Salmonella infections treated, 11 had satisfactory results, 5 unsatisfactory, and 3 indeterminate; of 57 Shigella infections, 44 responded satisfactorily and 8 unsatisfactorily. Bettag et al.[40] treated 30 typhoid carriers with a combination of oral and intramuscular drug; they felt that preliminary results were encouraging and that kanamycin was the most promising drug they had used to date. A chronic Salmonella infection was treated with combined parenteral and oral kanamycin with good results.[16]

In general, there have been relatively few side-effects with oral kanamycin therapy; some patients have had diarrhea, but only rarely has it been necessary to discontinue treatment (two patients receiving 8 gm. of base activity daily were in this category,[36] whereas others have tolerated 12 gm. daily). Nausea and vomiting are apparently very rare.

2. *Parenteral Use.*—In addition to the aforementioned cases of intestinal infection treated orally or with combined therapy, there are a number of cases treated with intramuscular kanamycin alone by a number of different investigators. Sixteen typhoid carriers were treated, with preliminary results considered encouraging.[41] Four cases of typhoid were treated, with only one patient showing a good response,[10,28] three

patients with paratyphoid disease were treated, two with good results.[10,35]

One Salmonella infection not responding to chloramphenicol (Chloromycetin) was handled adequately with the addition of kanamycin.[9] Four patients with Shigella sonnei infection were treated by Riley[42] with good results; this author also had good responses in one case each of E. coli gastroenteritis and staphylococcal enteritis treated with intramuscular kanamycin. Yow and Womack[43] had good results in the treatment of six cases of staphylococcal gastroenteritis (some with staphylococcal disease elsewhere as well).

One case of Salmonella panama subacute bacterial endocarditis was managed successfully with parenteral kanamycin.[44]

Table 4 is a summary of the type of infections (by organism) treated with kanamycin and the results generally obtained. Final judgment as to efficacy in some of these conditions must be reserved until more cases are treated or until there is further follow-up on those already treated. In some cases, tuberculosis, for example, the type of case material (for example, chronic far-advanced cavitary disease) was such as to preclude very striking responses to any drug. Again, kanamycin is likely to prove useful in combination with other drugs for the treatment of some patients with tuberculosis. It is important to remember that a good response does not necessarily imply an optimum response (for example, E. histolytica carrier state) or that kanamycin is the drug of choice (although pneumococcal, streptococcal, and gonococcal infections sometimes respond to kanamycin, they respond consistently to another agent which is less toxic). Conversely, although most Pseudomonas infections and cases of typhoid were frank treatment failures on kanamycin, a few of these difficult infections did respond well to the drug, and so it will be of value in those types of cases at times. Finally, although Proteus infections are listed under "Sometimes Responded," it is likely that kanamycin is the most effective single antibiotic against Proteus.

TABLE 4.—*Clinical Response of Various Infections to Kanamycin*

Usually Responded *	Sometimes Responded	Usually Treatment Failures
Mimeae infections †	Pneumococcal infections	Brucellosis
Tularemia †	Group A β-hemolytic streptococcic infections	Pseudomonas infections
Atypical acid-fast bacillus infections	Typhoid carrier state	Typhoid fever
Staphylococcal enteritis †	Proteus infections	Mycotic infections
Staphylococcal infections, other	Paratyphoid fever †	Anaerobic infections
E. coli gastroenteritis †	Gonorrhea	
E. coli infections, other	Tuberculosis	
Aerobacter-Klebsiella infections		
Paracolon infections		
Shigella dysentery		
Salmonella enteritis		
Chronic Shigella and Salmonella infections		
Alcaligenes infections†		
Anthrax		
Amebiasis †		
E. histolytica carrier state		

* This does not imply that kanamycin is necessarily the drug of choice or that the response is optimum (data obtained from References 9-16, 22, 23, 25, 28, 35, 38-51).

† Very few cases reported.

To return to consideration of kanamycin in tuberculosis, Donomae et al.[50] treated 110 cases of pulmonary tuberculosis with kanamycin plus PAS and felt that results were almost equivalent to a streptomycin-PAS regimen. They indicated that kanamycin was effective in patients resistant to one or more combinations of streptomycin, isoniazid and PAS and found that kanamycin could be used safely in two patients strongly allergic to streptomycin. The toxicity of kanamycin is such that prolonged treatment with 1 gm. or more daily is not feasible; further work is needed on regimens employing the drug two or three times weekly.

Clinically, results of kanamycin therapy of a variety of infections caused by Gram-negative bacilli (except Brucella, Pseudomonas, and S. typhi) have been very encouraging. This includes several cases of serious bacteremia, some with shock. Be-

cause of its broad spectrum of activity and its bactericidal activity, kanamycin should probably be regarded as the agent of choice in patients who clinically have Gram-negative bacteremia (and also those who clinically have a bacteremia which could be either a Gram-negative bacillary infection or staphylococcal in origin) and in whom definitive bacteriological diagnosis and/or sensitivity test results are not yet available. This is certainly not meant to encourage irrational or hasty "shotgun" therapy of patients with undiagnosed fevers, etc. But it is not uncommon in hospital practice to encounter a seriously ill patient with chills and fever, hypotension or frank shock, and a background history which would make him a likely candidate for a bacteremia (as, for example, recent genitourinary tract manipulation). In such a situation it is imperative to begin antibacterial therapy immediately. Obviously, appropriate bacteriologic and other studies should be initiated prior to instituting therapy. Furthermore, if the clinical picture or recent cultures of urine or other material from a likely portal of entry for the bacteremia indicate the likelihood of pneumococci, streptococci, Pseudomonas, or any other kanamycin-resistant organism as a cause of the infection, then kanamycin is certainly contraindicated.

Kanamycin is one of the more effective agents available for the treatment of staphylococcal infections. It has given good responses in a number of serious staphylococcal infections, including bacterial endocarditis, septicemia, and pneumonia. Administration of kanamycin intramuscularly and by aerosol led to improvement in patients with chronic pulmonary infections secondary to cystic fibrosis of the pancreas.[29]

The results in three cases of meningitis[28,45] were poor, but it would not be proper to judge the potential of kanamycin in this type of infection on these cases. Two of the infections were due to Aerobacter aerogenes, and in one the organism was eliminated and the cell count lowered. The third case was due to a Staphylococcus pyogenes var. aureus, and there were many complicating features. Nevertheless, in view of the fact that kanamycin does not diffuse into the spinal fluid to any extent in patients with uninflamed meninges, it is possible that it would have to be given intrathecally in order to be effective. It has been given intrathecally in one patient with meningitis[9]; this patient had subdural bleeding and died, with the role of the infection in her terminal state uncertain; further details are not given, and the dose of intrathecal kanamycin and the presence or absence of side-effects are not discussed. It is unfortunate that data are not yet available on spinal fluid levels of kanamycin after intramuscular administration to patients with meningitis.

Results in brucellosis are nil—several cases have been treated with complete lack of clinical or bacteriologic response.[28,38,44]

Two cases of Bacteroides infections have been treated, with no response, and Bacteroides has been recovered from other patients after kanamycin therapy for other types of infections.[35] It is unlikely that any other type of anaerobic infection would respond.

Although fungal infections have not been treated to any extent with this agent, it would not be expected to be effective, and yeasts have appeared after elimination of other organisms with kanamycin therapy.

Results of kanamycin treatment of various genitourinary infections, and particularly pyelonephritis, are encouraging. Further work is necessary for a better evaluation in this field; the more widespread use of quantitative urine cultures would aid in interpretation of the data, and, in particular, long-term bacteriologic follow-up of treated patients who have responded well is going to be extremely important. Infections that have generally responded well (at least as far as immediate post-treatment cultures are concerned) include those due to E. coli, A. aerogenes, paracolons, intermediate coliforms, Alcaligenes, S. aureus, and, to a less extent, Proteus. Pseudomonas

and enterococci have seldom responded and have often appeared as superinfecting organisms along with Candida and Bacteroides.[11,16,23,35,38,46,51] Follow-up studies in 13 of my patients[35] who had a good bacteriologic response during and at the end of treatment with kanamycin showed that 4 patients relapsed between 1 and 10 weeks after discontinuance of the drug and that, at the time of the last review of records, 6 had been followed at least 1 month with no relapse (3 of these had been followed at least 12 weeks). Of particular interest is the demonstration by Yow and Monzon[16,52] of healing of pyelonephritis by serial intravenous pyelograms and renal biopsies.

Kanamycin has been administered by a variety of routes other than oral and intramuscular. Small numbers of patients have received the drug intravenously with good tolerance and no evidence of increased toxicity.[25,35] The drug is apparently compatible with the usual solutions administered intravenously. We have preferred, on theoretical grounds, to administer kanamycin by slow drip when giving it intravenously; with certain other drugs, high blood levels (whether due to rapid infusion or to other things) have been associated with toxicity.

Intrapleural administration of kanamycin has been used by several investigators.[9,13,16,43] The drug has been tolerated well in concentrations of 2.5 mg. per milliliter and in total daily doses of 1.0 gm. As many as 44 instillations over a period of 11 days have been given to one patient. It was not always possible to assess the effectiveness because of adjunctive therapy, but at times intrapleural kanamycin has effectively sterilized the pleural space; one patient failed to respond.

The intrathecal use of kanamycin in one patient has been referred to previously, in connection with treatment of meningitis. Kanamycin has been instilled into the ventricular cavity[16,43] in a concentration of 2.5 mg. per milliliter, with no evidence of local irritation.

Animal studies[53] indicated that intraperitoneal kanamycin was very well tolerated and was safer than intraperitoneal neomycin in high dosage (in rabbits and dogs). In these animals, satisfactory serum levels were obtained one hour after intraperitoneal administration. Kanamycin has been tolerated well intraperitoneally in humans, in a concentration of 2.5 mg. per milliliter and in a total dose of 0.5 gm.[16,31] Serum levels after intraperitoneal administration to humans are not available, and available data do not allow proper evaluation of possible therapeutic benefits derived from such administration.

Because kanamycin administered intramuscularly does not give effective levels in bronchial secretions ordinarily, High et al.[13] and Huang et al.[29] have given the drug by aerosol or by both routes concurrently for various bronchopulmonary infections, including those associated with cystic fibrosis of the pancreas. The drug was always well tolerated and appeared to be effective when administered as an aerosol. The drug was given in amounts up to 300 mg. in a single treatment for up to 24 days and up to 72 aerosol treatments in all. Some patients have received as many as seven courses of aerosol kanamycin. Kanamycin concentrations in the serum were small or absent after aerosol administration, but good levels were obtained in bronchial secretions.

Finally, kanamycin has been used topically or as an irrigating fluid in superficial lesions and wounds by many workers.[11,16,25,38,43,54,55] It has been used as an ointment, as a cream, and as a solution in concentrations varying from 2.5 mg. per milliliter (or per gram) to 30 mg. per milliliter (or gram). There has been no evidence of irritation and no clear-cut evidence of allergenicity to date, and results, where they could be evaluated, seem to be generally good. One patient has received kanamycin solution as eye drops, with no evidence of irritation.[30]

Toxicity

The most important type of toxicity noted with parenteral kanamycin therapy was damage to the eighth nerve. This has been

noted by a number of investigators * and has involved both auditory and vestibular functions, but chiefly the auditory. Many of the reported cases of auditory damage have been documented by serial audiographic studies, but some have been clinical diagnoses based on the appearance, in association with kanamycin therapy, of tinnitus, impairment of hearing, or both. Some patients have had only high-tone loss (above the speech frequencies), noted on audiograms, without subjective hearing loss. To date, 27 patients † have had persistent conversational hearing loss as a result of kanamycin therapy; two patients with mild hearing loss documented clinically and by serial audiograms reverted to pretreatment levels (except for 8,000 cycles in one of these patients) after the drug was discontinued.[38,56] Some patients have had severe bilateral hearing loss, a few to the extent of total or virtually total deafness (even to audiographic testing). Most patients had bilateral auditory damage, but some had unilateral. The higher frequencies (especially 4,000 and 8,000 cycles, which are above the speech range, but to less extent 2,000 cycles, which is in the upper speech range) were involved more frequently than the others. Several workers [11,35,49,56] have indicated that conversational hearing loss may be prevented by doing serial audiograms and stopping the drug if high-tone loss (which may precede severer damage) appears during therapy. Furthermore, tinnitus is often (but, unfortunately, not always) an important early warning of auditory damage, and so permanent damage may be avoided at times by stopping the drug promptly on appearance of this symptom.[35,38,49,56] One encouraging thing about the eighth nerve toxicity of kanamycin (in comparison with neomycin and dihydrostreptomycin) is that so far there has been little evidence of progression of damage for long periods after the drug has been stopped. One exception is the case reported by Frost et al.[56]; this patient received 40 gm. of kanamycin (0.5 gm. b. i. d., 15 mg. per kilogram of body weight per day), and his hearing suddenly and rapidly deteriorated. At this time the blood urea nitrogen (initially 18 mg. %) was found to be 82 mg. %. Although the drug was immediately discontinued, the hearing impairment became progressively worse over the next three weeks, with eventual total deafness, bilaterally. It is likely that this patient had impaired renal function for some time before and after the determination of the BUN of 82 mg. %, and therefore undoubtedly had high, persistent kanamycin serum levels. Another possible exception is the patient reported by Duke et al.[45] who developed tinnitus six weeks after completion of kanamycin therapy; this patient failed to appear for study and follow-up.

Several factors have been found to predispose to eighth nerve damage. Table 5 shows that there was a statistically significant correlation between average total dose in grams and average daily dose in milligrams per kilogram of body weight and eighth nerve toxicity. There was no statis-

TABLE 5.—*Effect of Dose and of Patients' Age on Toxicity of Kanamycin* [31]

	Average Total Dose, Gm.	Average Daily Dose, Mg/Kg. Wt.	Average Days Therapy, No.	Average Age
Total group (106 patients)	28.2	27.6	15.6	52.9
Patients with eighth nerve toxicity (22 patients)	46.7	36.0	20.3	50.8
Patients with no eighth nerve toxicity (84 patients)	23.3	25.2	14.6	53.4
Probability comparison of above 2 groups, P *	$P<0.001$	P 0.001	P 0.1	P 0.4
Patients with elevated creatinine due to kanamycin (12 patients)	38.8	29.8	19.1	64.2
Patients with no elevation of creatinine (94 patients)	27.2	26.2	15.4	51.5
Probability comparison of above 2 groups, P *	P 0.1	P 0.3	P 0.1	P 0.001

* P 0.01 or less indicates statistically significant difference between 2 groups being compared.

* References 7, 11, 12, 15, 16, 35, 38, 45-50, 56.
† References 7, 11, 12, 15, 16, 35, 38, 46-50, 56.

tically valid correlation between duration of therapy and such toxicity, but there may well be a trend in that direction. There was nothing in our data to support the statements of some workers that older people and people with previous hearing loss are more susceptible to eighth nerve damage from kanamycin. Our data [35,38] indicate that the correlation between dosage of kanamycin and eighth nerve damage holds true also in analysis of the severity of the eighth nerve damage. Thus, only one of nine cases of eighth nerve toxicity, occurring in patients treated with 30 mg. per kilogram of body weight per day or less, was classed as of moderate severity, the other eight being mild; the moderately severe case had been treated for 84 days. Donomae [50] and Ichikawa [11] also present data to back up a correlation between dosage of kanamycin and ototoxicity. Ichikawa feels that auditory damage is related to the total amount of drug administered rather than to the schedule of treatment, and so administration of the drug twice weekly rather than daily (in the treatment of tuberculosis) would not decrease the toxicity encountered with any given total dose; I feel that further data are required to establish this point. There is a definite association between impaired renal function and increased incidence of ototoxicity.[35,38] In our latest study,[35] 22 patients showed eighth nerve toxicity, and, of this number, 9 had definitely impaired renal function (not necessarily due to kanamycin) and 2 had possible renal impairment. In contrast, among 84 patients without ototoxicity, only 16 had impaired renal function. In other studies,[11,46] two of six and three of six, respectively, patients with ototoxicity had impaired renal function; however, these authors do not indicate the incidence of renal impairment in their patients who did not develop eighth nerve damage. The suggestion has been made [38] that other ototoxic drugs might act in an additive way with kanamycin (even if not given concurrently); the importance of watching for this possibility is emphasized by the report by White and Knight [12] of a patient who received a long course of streptomycin therapy and then became almost completely deaf after only 11 days of treatment with streptomycin and kanamycin in combination.

Eleven cases of vestibular damage incident to kanamycin therapy have been reported.[7,12,35,48,50,56] Some of these cases were associated with audiographic damage; others, with tinnitus only. Results of caloric tests did not always correlate with clinical evidence of vestibular toxicity. Details are lacking on most of the reported cases, but it appears that the vertigo was generally mild to moderate and of short duration. At least two cases have required assistance in walking, however,[35,56] and at least one case had considerable difficulty for five months.[35]

The next major manifestation of kanamycin toxicity is the nephrotoxicity. With the possible exception of one case of acute renal insufficiency, reported by Berman and Katz,[57] the nephrotoxicity has been important only as it predisposed the patient to eighth nerve damage (as discussed previously). Virtually all reports on the use of kanamycin mention urinary sediment abnormalities. Although the incidence of such abnormalities is considerable, these changes were generally very mild, were often present only intermittently, and were not correlated at all with more important evidence of nephrotoxicity (nitrogen retention).[35] Albumin seldom was present in more than "1+" amounts. Hematuria usually consisted of only occasional red blood cells per high-power microscopic field; casts, usually of the fine granular variety, were present in similar numbers. Follow-up of patients showing urinary sediment abnormalities revealed that in most cases the abnormal findings disappeared within one week of discontinuance of therapy but that a few patients had abnormalities persisting for two to three weeks.

Several authors have reported impairment of renal function (generally indicated by nitrogen retention) attributable to kana-

mycin therapy.‡ The rises in serum creatinine or blood urea nitrogen have generally been mild (provided therapy is promptly stopped). After the drug is discontinued further rises seldom occur beyond one week, but one patient showed a definite progressive rise over a period of 19 days post treatment.[35] It is important to note that serum creatinines generally did not return to normal or pretreatment values until three or four weeks after treatment was stopped and that in a few cases elevated creatinines persisted considerably longer.[35] Winfield et al.,[58] using large doses, demonstrated impairment of one or more of the following functions in each of 20 patients studied: clearances of inulin, creatinine, and *p*-aminohippurate, maximal urinary concentrating ability, and phenolsulfonphthalein excretion.

Table 5 shows a statistically significant correlation between age and nephrotoxicity due to kanamycin, older patients being more susceptible to the damage. Although there was no significant correlation between nephrotoxicity and dosage or duration of therapy, there may be some trends in that direction. In our study,[35] only 2 patients of 55 treated for two weeks or less had a definite rise in creatinine, and only 1 of 40 treated with 20 mg. per kilogram of body weight per day or less had creatinine elevation.

A reported case of oliguria[57] has been mentioned earlier in this report. This patient had been treated with 25 mg. per kilogram of body weight per day of kanamycin for two weeks and was doing very well when he experienced fever, delirium, and oliguria; the authors felt that kanamycin was responsible, and they discontinued the drug. In the apparent absence of other significant changes in management, the patient responded well, with an increase in urine output from a low of 15 ml. per day to 1,650 ml. in three days. Renal biopsy 25 days after onset of the oliguria revealed findings characteristic of acute tubular necrosis.

‡ References 11, 15, 35, 38, 42, 46, 48, 49.

Although many authors noted a significant percentage of kanamycin-treated patients exhibiting eosinophilia (generally 8% to 10% of the cells in a differential count), there was generally no other indication of allergy in these patients, and a few patients with clinical allergy did not manifest eosinophilia. Cross sensitivity with related drugs is suggested by a patient, previously exhibiting a rash after topical neomycin therapy, who developed a rash after intramuscular kanamycin and had positive immediate skin tests to neomycin, kanamycin, and streptomycin.[38] There are also two patients who had previously had rashes with streptomycin therapy who developed pruritus (without rash) on kanamycin.[22] Conversely, Donomae[50] reports two patients who could not take streptomycin because of hypersensitivity who tolerated kanamycin perfectly well. Several other authors have described rashes in patients receiving kanamycin.[11,25,45]

The rashes have generally been maculopapular, have been readily controlled with antihistamines while therapy is being continued, and at times have disappeared in spite of continued therapy. Other reported hypersensitivity phenomena include one of drug fever, one of suspected hydrops of the labyrinth (after one injection), and one of possible anaphylactic reaction.[38]

There have been a few bizarre reactions, all minor and not necessitating discontinuance of therapy, indicative of neurotoxicity —circumoral numbness,[22] numbness and paresthesias elsewhere,[38,50] restlessness and headaches,[50] and odd visual complaints with no objective findings.[38] There was one questionable case of peroneal palsy.[38]

One case of diarrhea, nonspecific in nature and clearly related to kanamycin, has been described.[35] One case of nonspecific stomatitis is recorded.[22] There is also one case of Pseudomonas proctitis after the use of kanamycin.[10]

Moderately severe local pain sometimes follows the intramuscular injection of kanamycin despite the addition of local anesthetic agents. Occasionally nodules will form at

the injection site, and two sterile abscesses at the injection site have been reported.[45]

Dosage and Precautions

Suggestions as to dosage and precautions to be observed in administering kanamycin are incorporated in the Appendix.

Conclusions

Kanamycin is a new, bactericidal antibiotic which has been shown to be highly effective when given parenterally in the treatment of a number of resistant staphylococcal and Gram-negative bacillary infections. Used orally, it exerts a profound effect on the normal aerobic intestinal flora and has been effective or shown promise in the management of some intestinal infections and carrier states. It is relatively or totally ineffective in infections due to pneumococci, streptococci, various anaerobes, Pseudomonas, and fungi.

Toxicity inherent in the drug can be avoided or minimized with careful management. Factors predisposing to toxicity are considered in detail; early signs of toxicity are emphasized, and certain precautions to be observed are suggested.

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Appendix

Suggestions for Avoiding Toxicity with Parenteral Use of Kanamycin

1. Dosage should be in terms of milligrams per kilogram of body weight. On the basis of present information, 15 mg. per kilogram per day would seem to be adequate generally, and it may be that even smaller doses would be effective. Larger doses may be indicated for the first day or two of therapy in seriously ill patients and in other special situations.

2. Duration of therapy should not be unnecessarily extended.

3. Patients should be questioned daily with regard to tinnitus, and appearance of this symptom in a patient who has not previously had it or aggravation of preexisting tinnitus makes it mandatory to discontinue therapy if at all possible.

4. Serial audiograms should be obtained (one prior to therapy, then every one to two weeks, and finally one week after therapy is discontinued) where feasible. The drug should be discontinued if any significant changes are noted.

5. Where it is necessary to administer kanamycin to patients with impaired renal function extreme caution should be observed. Dosage should be reduced and, where possible, guided by serum drug level determinations. (Impaired renal function may actually improve on kanamycin when related to pyelonephritis, bacteremic shock, etc.)

6. Renal function should be followed closely during the treatment period; serum creatinine, nonprotein nitrogen, or blood urea nitrogen determinations should be obtained three times weekly. Impairment of renal function, as indicated by the above or other tests, or an unexplained decrease in urinary output are indications for reduced dosage or discontinuation of therapy.

7. Care should be exercised in the treatment of elderly patients because they are more subject to nephrotoxicity and because they, at times, get relatively high serum levels.

8. One should avoid concurrent or sequential use of kanamycin and other ototoxic drugs, such as neomycin, vancomycin, streptomycin or dihydrostreptomycin, and viomycin, and, where possible, of kanamycin and other agents that are nephrotoxic.

9. Patients should be well hydrated. Consideration should be given to administering kanamycin in reduced dosage in patients who are dehydrated.

Increased Spinal Fluid Protein in Hyperparathyroidism and Other Hypercalcemic States

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The finding of hypercalcemia is usually considered adequate explanation for otherwise unexplained central nervous system manifestations, as indicated by Fitz,[1] Bogdonoff,[2] and others.[3,4] Recently, however, the medical service of this hospital was faced with the problem of a patient with hypercalcemia and disordered central nervous system function who also had significantly increased cerebrospinal fluid (CSF) protein. This latter finding directed the investigators away from the proper diagnosis of hyperparathyroidism and from the resolution to perform emergency surgical exploration of the neck. The patient died during the period of diagnostic study, and at autopsy he was found to have two parathyroid adenomas with no other cause for the CSF abnormality. We have since observed another patient with hypercalcemia, secondary to carcinoma of the pancreas, and central nervous system manifestations, who also had increased CSF protein. Our experience with these cases is being reported, together with a review of three previously published cases, to draw attention to the possibility that elevation of the CSF protein can occasionally be a feature of the hypercalcemic state without coexisting evidence of organic brain disease.

Report of Cases

CASE 1.—A 62-year-old white man was transferred to the neurosurgical service of the McKinney Veterans Administration Hospital on Nov. 15, 1956, because of a suspected pituitary adenoma. His illness began insidiously with anorexia, weight loss, and weakness during the first six months of the year preceding admission. During the six months immediately preceding entry he had experienced profound anorexia and loss of 60 lb. in weight. His only other gastrointestinal complaints were long-standing constipation and a vague account of having passed black stools two months prior to admission. He complained of constant fatigue, and his family noted him to be increasingly irritable, confused, and drowsy. A partial thyroidectomy had been performed 26 years previously, but the indications were unknown. Four years before admission a transurethral prostatectomy was performed for benign hyperplasia, and one year preceding admission a nevus had been removed from his back without an accompanying pathological examination.

Beginning in August, 1956, he had three hospital admissions prior to arrival at this hospital. In the first hospital his white blood cell count was 20,000 per cubic millimeter; x-rays of the gallbladder and gastrointestinal tract were normal, and the bone marrow was normal on smear. Despite the normal bone marrow, a presumptive diagnosis of multiple myeloma was made. At the second hospital he was found to be confused and chronically constipated and to have polydipsia and polyuria. The neck was stiff, and one examiner found the left arm reflexes to be more active than those of the right arm and Babinski's and Hoffman's signs to be present on the left. The leukocyte counts varied from 13,000 to 19,000 per cubic millimeter. The hemoglobin was 14.3 gm/100 cc. on admission but fell to 12 gm/100 cc. two weeks later. The urine was normal except for a trace of protein, and the alkaline phosphatase was normal. X-rays of the long bones and skull were interpreted as demonstrating demineralization and slight deepening of the sella turcica. Two lumbar punctures revealed CSF protein values of 175 and 140 mg/100 cc., with no other abnormalities. An electroencephalogram was interpreted as follows: "Diffusely slow electrogram with more slow activity in the frontal leads, particularly on the left side." A presumptive diagnosis of melanosarcoma with cerebral metastases was made. He was then transferred to the neurology service of a

Submitted for publication Nov. 5, 1958.

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TABLE 1.—*Laboratory Observations, Case 1*

Observation	Nov. 1956				Dec. 1956						
	23	26	27	29	1	3	4	10	12	13	14
Serum calcium, mg. %	18.4	16.1	17.9	16.8	15.1	14.6	13.8	18.2	18.6	20.5	19.3
Serum phosphorus, mg. %	4.3	5.1	5.6	5.4	3.2	4.0	2.3	5.3	5.6		4.4
Alkaline phosphatase, B. U.	9.7	8.9	6.7	12.1			10.4				
Serum sodium, mEq/L			126	128	129	133	132	134	133		132
Serum potassium, mEq/L			3.2	3.9	3.3	3.6	4.4	3.6	3.4		5.4
Blood urea N, mg. %				45	34	23	20	25	28	32	39
Serum albumin, gm. %	4.5	4.1									
Serum globulin, gm. %	2.5	2.5									
White blood cells, 1,000/cu. mm.	16.3			29.4							41.2
Hemoglobin, gm. %	11.8			11.5							10.1
Urine volume, L/24 hr.		1.2	2.3		4.6	3.9	2.9	6.4	4.1	5.5	
Urine calcium, mg/24 hr.		208				361					

third hospital, on Nov. 3. There he was found to be confused, weak, and emaciated. The deep tendon reflexes were slightly more active on the left than on the right, and there was a Hoffman's sign on the left. The white blood cell count was 16,600 per cubic millimeter; hemoglobin, 10.6 gm/100 cc., and urine, normal. An electroencephalogram was considered to be abnormal owing to diffuse slowing of activity. On the basis of skull x-rays which were interpreted as revealing demineralization and possible deepening of the sella turcica, a diagnosis of suspected pituitary adenoma was made, and he was transferred to this hospital.

Physical examination revealed an emaciated, dehydrated, lethargic, confused man who fell asleep several times during the examination. The blood pressure was 140/80; pulse, 90, and temperature, 98 F. The skin was dry, wrinkled, and deeply pigmented, and the mucous membranes and the tongue were dry and wrinkled. The pupils and optic fundi were normal. The neck was slightly stiff, and there was an old surgical scar in the thyroid area. The thyroid gland could not be palpated, and no masses or lymph nodes were felt in the neck. The heart and lungs were normal. There was plasticity of the muscles of the extremities, with bone tenderness over the distal ends of the ulnas and fibulas. He complained of pain in the legs and could barely lift them from the bed because of weakness. All deep tendon reflexes were active, but those on the left were increased over those on the right. No pathological reflexes or sensory disturbances were detected.

A number of pertinent laboratory data are listed in Table 1. Other significant observations were as follows: urinalysis, 1+ protein, no Bence-Jones protein; serological test for syphilis, negative; differential white blood cell count: neutrophils, 81%, monocytes, 9%, eosinophils, 6%; hematocrit, 32%; erythrocyte sedimentation rate, 26 mm. in one hour (Wintrobe); serum acid phosphatase, 2.5 King-Armstrong units; bone marrow examination, normal; serum bilirubin, 1.0 mg/100 cc.; serum cryoglobulin, negative, and serum protein electrophoresis, normal pattern.

X-ray interpretations included skull, with planigrams of the sella turcica, normal except for demineralization; intravenous pyelograms, no visualization of the kidneys; esophagus, stomach, and duodenum, minimal deformity of the duodenal bulb; chest, normal; dental films, intact lamina dura, and long bones, small punched-out areas in the tibias and fibulas. An electrocardiogram revealed increased intraventricular conduction time, with prolongation of the Q-T interval and depression of the S-T segment in lead V_4. On the day of death there was shortening of the Q-T interval.

The patient was transferred to the medical service on Nov. 23, after x-ray studies had demonstrated the presence of a normal sella turcica. On the same day the laboratory reported the serum calcium to be 18.4 mg/100 cc. He remained weak, confused, and lethargic until his death. Hyponatremia and dehydration persisted despite the daily administration of 8 to 16 gm. of sodium chloride and 3 to 4 liters of fluid. Examination of the cerebrospinal fluid, on Nov. 26, revealed normal pressure, xanthochromia, and protein of 159 mg/100 cc., with no increase in cells. On Nov. 29, the blood urea nitrogen was 45 mg/100 cc., but with vigorous hydration for the next several days the level fell to normal. Coincident with the fall in blood urea nitrogen the serum calcium fell to 13.8 mg/100 cc. and the inorganic phosphorus to 2.3 mg/100 cc., and there was temporary clearing of the sensorium. For several days he was able to take food and liquids by mouth, but on Dec. 9, he again became confused, and on the following day the serum calcium was found to be 18.2 mg/100 cc. Thereafter, despite the intake of 6 to 7 liters of fluid daily and urine output of 4 to 6 liters daily, there was further rise in the serum calcium level. Beginning on Dec. 10, he was given 150 mg.

of cortisone acetate intramuscularly daily for three days, without effect on the serum calcium. He was also given large amounts of sodium citrate intravenously, without benefit, during this stage of illness. Death occurred on Dec. 14, as a result of cardiac arrest.

At postmortem examination a parathyroid adenoma, 24 mm. in diameter, was attached to the left inferior pole of the thyroid gland, and another, 10 mm. in diameter, was attached to the right inferior pole. The larger adenoma consisted of loosely arranged chief cells with scattered foci of necrosis, while the smaller adenoma consisted of chief cells in a predominantly tubular arrangement. In the midportion of the left lobe of the thyroid there was a small papillary adenocarcinoma. Sections from the ribs, ileum, vertebrae, and skull revealed osteitis fibrosa. There was no metastatic calcification of soft tissues. The brain, pituitary gland, pancreas, and adrenal glands were normal, both grossly and microscopically.

Comment.—Hypercalcemia of the degree exhibited by this patient, in the absence of some other obvious cause, would ordinarily have been ascribed to hyperparathyroidism in this hospital, even with normal serum inorganic phosphorus and preservation of the lamina dura. That such a diagnosis was not made and the patient subjected to surgical exploration of the neck was attributable to the influence of the significantly elevated spinal fluid protein on the thinking of the hospital staff. This was thought by some observers to be indicative of cerebral metastases from some malignancy capable of exerting a parathyroid hormone-like effect.[4,5] Another seriously considered diagnosis was multiple myeloma, even though there was no evidence from bone marrow and serum protein studies to support that impression. Sarcoidosis was still another possibility, but nothing other than the hypercalcemia suggested that diagnosis. Cortisone was begun in the hope of lowering the serum calcium, but the patient's condition deteriorated before an adequate trial was completed. It is safe to assume that the calcium level would not have been influenced by cortisone had he lived long enough for the trial to be completed. This would have been strong evidence against the diagnosis of sarcoidosis, but it would not have permitted differentiation between hyperparathyroidism and a malignancy, since the hypercalcemia associated with hyperparathyroidism is unaffected by cortisone, while that associated with malignant disease is reported by Connor et al.[6] to respond in a variable manner.

In retrospect, the spinal fluid findings should have been ignored and surgical exploration recommended despite the complication of renal insufficiency. The potential harm from an unnecessary operation on a patient with cerebral metastases, multiple myeloma, or sarcoidosis is negligible in comparison to the consequence of not operating on a patient with severe hyperparathyroidism and serum calcium levels approaching the lethal range. Unfortunately, undue weight was given to the spinal fluid protein because it was not known at the time that significant elevations can occur in hypercalcemic states.

The association of a small papillary adenocarcinoma of the thyroid with hyperparathyroidism in this case was probably coincidental, although Ogburn and Black[7] reported that 4 of 230 cases of hyperparathyroidism seen at the Mayo Clinic had coexisting papillary adenocarcinomas of the thyroid gland.

Case 2.—A 63-year-old white man entered the McKinney Veterans Administration Hospital on May 1, 1958, three months after onset of weight loss, lethargy, polydipsia, and polyuria. Five weeks before admission he was discovered by his private physician to have glycosuria and hyperglycemia, for which he was treated ineffectively with tolbutamide. In the week prior to hospitalization he became weak, apathetic, and confused; ceased taking fluids, and lapsed into semistupor. Examination revealed evidence of recent weight loss, severe dehydration, and confusion. The deep tendon reflexes were brisk and symmetrical.

Laboratory observations were as follows: white blood cell count, 10,700 per cubic millimeter; differential white cell count, normal; hemoglobin, 16.7 gm/100 cc.; urine, normal except for 3+ Sulkowitch test; serum calcium, 16.3 mg/100 cc.; serum inorganic phosphorus, 2.5 mg/100 cc.; alkaline phosphatase 4.9 Bodansky units/100 cc.; blood urea nitrogen, 21 mg/100 cc., and fasting blood sugar, 182 mg/100 cc. The spinal fluid, examined May 2 and May 7, was normal except for protein contents of 65 and 80 mg/100 cc., respec-

tively. X-ray examinations of the skull, chest, spine, pelvis, ribs, and kidneys were normal.

The patient's condition steadily deteriorated. On May 3, bronchopneumonia developed and he lapsed into coma. Emergency neck surgery was then performed, with negative results. After surgery he was alternately stuporous and comatose until his death, on May 12. The serum calcium level varied from 13.4 to 16.3 mg/100 cc. even though he was given hydrocortisone and the urine volume was kept between three and six liters per day. The urinary calcium excretion was 1,020, 1,080, and 814 mg/24 hours on three separate determinations during a period when there was no calcium intake.

Autopsy disclosed an adenocarcinoma of the tail of the pancreas with hepatic metastases. Examination of the neck and mediastinum failed to reveal a parathyroid adenoma. The brain was normal.

Comment.—This patient had a malignant neoplasm that apparently caused the clinical manifestations of hyperparathyroidism. Under the circumstances, the combination of central nervous system abnormalities and increased cerebrospinal fluid protein would ordinarily be considered indicative of cerebral metastases, as suggested by Myers.[8,9] However, the finding of a normal brain at autopsy again raised the question of a direct relationship between hypercalcemia and elevation of the spinal fluid protein.

Review of Published Case Reports

In reviewing a large number of published case reports of hyperparathyroidism and other hypercalcemic states, which have appeared in the past 30 years, we have found 24 cases with serum calcium levels above 11.5 mg/100 cc. in which CSF protein determinations were recorded (Table 2). In four cases the values were greater than 60 mg/100 cc., but Moldawer's[10] second case must be discounted because there was also x-ray evidence of a pituitary adenoma.

In three cases there was no obvious explanation for the abnormal CSF protein. The patient reported by Schlesinger,[11] an infant with severe idiopathic hypercalcemia, had symptoms from birth, but hypercalcemia was not discovered until he was 7 month of age. At 4 months and 6 months, the CSF protein values were 110 and 65 mg/100 cc., respectively. Both the CSF protein and serum calcium levels eventually

TABLE 2.—*Cerebrospinal Fluid Protein Levels in Twenty-Four Reported Cases of Hypercalcemia*

Author	Case No.	CSF Protein, Mg/100 Cc.	Serum Calcium, Mg/100 Cc.	Diagnosis
Beare [21]		"Normal"	23.0	Hyperparathyroidism
Bogdonoff [2]	20	"Normal"	14.8-15.4	Hyperparathyroidism
Brenizer [14]	6	"Normal"	16.5	Hyperparathyroidism
Fitz [1]	1	65	14.0	Hyperparathyroidism
Fitz [3]	2	"Normal"	16.0-19.0	Hyperparathyroidism
Frost [23]		"Not remarkable"	12.8-14.3	Vitamin D intoxication
Kabakow [20]	2	"Normal"	13.8	Hodgkin's disease
Kaufman [17]		"Nonrevealing"	13.0-14.7	Vitamin D intoxication
Knuth [24]	1	44	12.4	Hyperparathyroidism
Lee [12]*	8	"Elevated"	20.0	Hyperparathyroidism
Mass. Gen. Hosp. Case [19]		"Normal"	13.7	Vitamin D intoxication
Moldawer [10]	1	54	12.8	Hyperparathyroidism, islet-cell adenoma
Moldawer [10]	2	113→80	13.8→10.2	Hyperparathyroidism, pituitary adenoma
Myers [9]		"Normal"	18.3-21.9	Lymphosarcoma
Oliver [30]		"Normal"	17.4 †	Hyperparathyroidism
Plimpton [4]	3	"Normal"	13-14.1	Hypernephroma
Pugh [31]		"Normal"	18.8	Hyperparathyroidism
Schlesinger [11]	4	110→"Normal"	14.3→"Normal"	Idiopathic hypercalcemia of infancy
Schneider [32]	7	"Normal"	15.5	Vitamin D intoxication
Schrumpf [26]		"Normal"	19.0-21.5	Hyperparathyroidism
Smith [34]		"Normal"	23.0	Hyperparathyroidism
Thomas [36]	3	"Normal"	17.3	Hyperparathyroidism
Walfe [38]	1	"Normal"	17.5	Hyperparathyroidism
Way [39]		"Normal"	12.0-15.0	Vitamin D intoxication

* Also reported by Harmon.[18]
† Postmortem determination.

returned to normal, although the exact time relationship was not indicated. This patient had a modest elevation of the blood urea, 85 mg/100 cc., but it is doubtful that this degree of urea retention significantly influenced the spinal fluid. Fitz's [1] patient (Case 2) had hyperparathyroidism and psychosis, with no explanation for either the psychosis or the increased CSF protein except the hypercalcemia.

The case reported briefly by Lee [12] and in detail by Harmon [13] presented a problem somewhat similar to that encountered in our first case. The record is of sufficient significance to warrant a brief abstract of Harmon's report.

A 6-year-old Negro boy was admitted to the Cincinnati General Hospital on Nov. 11, 1953, with listlessness, headache, aching extremities, vomiting, generalized abdominal pain, and painful stiffness of the neck and back of five days' duration. He had been chronically ill for 10 months, with intermittent and progressive stiffness of the knees, weakness of the legs, weight loss, and painful extremities. He was emaciated, dehydrated, irritable, and disoriented. The reflexes were hyperactive. The blood urea nitrogen was 43 mg/100 cc. on admission, but after hydration it fell and remained normal. There was a strongly positive Kahn test, which persisted throughout the hospital stay despite two courses of penicillin therapy. The family history was negative for syphilis, and the mother and siblings were serologically negative.

Initially, the CSF was clear but contained 45 mononuclear cells/100 cc.; the protein content was 44 mg/100 cc., and the Wassermann and gold curve reactions were negative. The patient sustained a grand mal convulsion on the fourth hospital day, and at that time the serum calcium was found to be 12.0 mg/100 cc. A repeat CSF examination revealed fewer cells, negative Wassermann and gold-curve reactions, and slight elevation of the protein content. On Nov. 24, the serum calcium and inorganic phosphorus levels were 16.8 and 6.2 mg/100 cc., respectively. Many diagnostic possibilities, including bacterial and fungal infections, collagen diseases, trichinosis, Weil's disease, and various encephalitides, were considered, but numerous laboratory studies failed to clarify the problem. He was sent to a convalescent home after a month, but rehospitalization was necessary, on Dec. 24, because of vomiting, headache, and semistupor.

The spinal fluid on readmission contained 68 mononuclear cells/100 cc. and protein, 72 mg/100 cc. For the next month periods of moderate well-being alternated with periods of lethargy, vomiting, and fever which progressed to coma and/or convulsions; the entire cycle lasting about 10 days and being repeated several times. Blindness was noted, and spasticity of the arms developed late in December. During this time the cellular response of the CSF paralleled the clinical condition but the protein content slowly rose to approximately 100 mg/100 cc. During January, 1954, the serum calcium ranged from 15.2 to 19.4 mg/100 cc. and the phosphorus remained under 6 mg/100 cc. After excision of a parathyroid adenoma, on Jan. 24, the patient had hypocalcemia, convulsions, and low serum magnesium, but after two weeks there was sustained clinical improvement. The CSF protein returned to normal, but the electroencephalogram was abnormal, and blindness and spasticity persisted. It was concluded that the diagnosis of syphilis was doubtful.

Comment.—In this case the evidence of central nervous system disease dominated the clinical picture to such an extent that the correct diagnosis was not made for several weeks, and permanent neurological damage resulted. It is significant that both the CSF cell count and protein content reverted to normal when the serum calcium level was corrected. In the light of this case, pleocytosis also must be considered as a possible manifestation of hypercalcemia.

Comment

Considering the frequency with which central nervous system manifestations are seen in the presence of hypercalcemia, it is surprising that so little attention has been paid to the CSF protein under such circumstances. Standard textbooks of medicine, neurology, and endocrinology and monographs dealing with hyperparathyroidism [5,14] and with cerebrospinal fluid [15,16] make no reference to the influence of hypercalcemia on the spinal fluid protein. Bartter,[17] in reviewing the relationship of the parathyroid gland to diseases of the nervous system, made no reference to the occurrence of increased CSF protein or pleocytosis in hyperparathyroidism. Madonick and Weissman [18] listed some of the less obvious conditions which have been reported to influence spinal fluid protein concentrations, including uremia, nephritis, Cushing's syn-

drome, myxedema, multiple myeloma without neurological signs, sarcoidosis without neurologic signs, rheumatoid arthritis, chronic alcoholism, history or findings of syphilis, history of lymphogranuloma venereum or positive Frei test, history of epilepsy, recent use of corticotropin (ACTH) or cortisone, and cerebral arteriosclerosis with complications but made no mention of hypercalcemia. They could demonstrate no significant influence of old age per se on the spinal fluid protein content, but Müller et al.[19] found a slight increase in normal persons with advancing age and suggested that values up to 60 mg/100 cc. in subjects over 60 should not be regarded as abnormal.

The changes in the CSF of patients with hypercalcemia are probably dependent upon the same mechanisms which are responsible for the central nervous system manifestations, such as psychosis, depression, disorientation, stupor, apathy, listlessness, lethargy, drowsiness, mental retardation, weakness, coma, convulsions, blindness, spasticity, and unequal reflexes and Babinski's sign, which have been listed by Bartter,[17] Harmon,[13] Thomas,[20] and others[1-3,21] as occurring in hypercalcemic states. The pathogenesis of these manifestations is unknown, but it has been suggested that they are caused by the precipitation of insoluble calcium phosphate in the brain as a result of exceeding the solubility product of calcium and phosphorus.[13,17] This is a plausible theory despite the infrequency of descriptions of calcium deposits in the brains of patients dying of hypercalcemia. However, Bauer and Freyberg[22] reported the finding of much lime salt in the dura mater and some in the pineal body of the brain of a patient who died of vitamin D intoxication, and Rogers[23] recorded gross calcification of the dura mater in his second case of hyperparathyroidism. Uremia and hypertension may be factors in some cases,[13,17] but the same clinical picture is to be seen in their absence. Other possible mechanisms which have been suggested include vascular spasm, multiple small hemorrhages, and magnesium deficiency.[13] Harmon[13] also mentioned the possibility of a demyelinating or fibrosing type of cerebral disease secondary to deposition of calcium phosphate or to hypercalcemia per se.

The possible role of convulsive seizures in causing spinal fluid protein elevation should also be examined. Since neither of our cases had convulsions and they were recorded in only one of the reported cases,[12] this could have been a factor in only one case. Moreover, Merritt and Fremont-Smith,[15] in a study of the CSF of 793 patients with convulsive seizures of unknown etiology, found the protein content to be under 45 mg/100 cc. in 90% of cases and over 85 mg/100 cc. in only 3 cases. Thus, convulsions per se appear to be an infrequent cause of elevations of CSF protein of the degree exhibited by Lee's patient.

Further observations will be necessary before the significance of the finding of elevation of the CSF protein in hypercalcemic states can be assessed. Nevertheless, such a finding should not deter the surgeon from exploring the neck of a patient suspected of hyperparathyroidism or from resecting an operable neoplasm. Myers' statement,[9] that elevation of the CSF protein in patients with hypercalcemia secondary to malignant disease is supporting evidence of central nervous system metastases, may not be valid.

Summary

Two cases are reported, in which elevation of the cerebrospinal fluid protein was found in patients with hypercalcemia, and three published case reports have been reviewed, in which there was the same association. Since no other cause for the abnormality of the spinal fluid was found in these five cases, it must be considered as a possible, though infrequent, manifestation of hypercalcemia. Failure to appreciate this possibility led to failure of diagnosis

and death in one of our cases and to delay in diagnosis and permanent neurological sequelae in one reported case. The pathogenesis of central nervous system manifestations and spinal fluid changes in hypercalcemic states is unknown.

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The Internist and Cardiac Arrest

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The principles of cardiac resuscitation have been formulated by Claude Beck.[1] The step by step procedure in the management of cardiac arrest is described in detail by Hosler in his excellent manual.[2] The roles of the surgeon and anesthesiologist in cardiac resuscitation are well known. The part of the internist has not been defined so clearly. It is the purpose of this paper to delineate the functions of the internist in the prevention and treatment of cardiac arrest.

Procedure and Results

Over 150 cases of cardiac arrest occurring in the Los Angeles area were collected in the two-year period, 1952-1954; of these, 132 were sufficiently documented for study.[3] Cardiac arrest was considered to be present when the heart beat was no longer strong enough to be of hemodynamic significance. In over 70% of the cases, the heart was in ventricular standstill. In 15% there was fluctuation between ventricular standstill and fibrillation. Fibrillation occurred as an initial arrhythmia in only four instances. In seven cases—all of whom recovered—the heart was still beating slowly and feebly. When arrest had progressed to ventricular standstill, the recovery rate was but 42%. When ventricular fibrillation was present, the recovery rate dropped precipitously to 17%.

Analysis of Time Intervals

Analysis of time intervals showed that treatment was started within four minutes of the time of diagnosis in 78 of the 132 cases. It is noteworthy that all 33 persons who recovered complete cardiac and cerebral function came from this group. The 45 who did not survive either died immediately or after days, weeks, or months in varying degrees of a decerebrate state. When there was over four minutes' delay in diagnosis or start of treatment—in 30 cases—only two patients survived; both of these show permanent central nervous system damage (they represent 1% of the total of 132). Correspondence with Veterans Administration facilities uncovered four more patients with permanent cerebral impairment secondary to cardiac arrest.[4] In 24 instances the observers disagreed or the time intervals could not be determined. It is likely that in these instances the interval between diagnosis and treatment was longer than four minutes, as none of these persons survived.

Since recovery occurred in only 33 cases and did not follow in 45 cases—even when prompt resuscitation was started within four minutes—these groups were compared to determine the additional differential factors in survival.[5]

Cardiorespiratory Embarrassment Prior to Onset of Complete Arrest

Premonitory evidence of cardiorespiratory embarrassment prior to the onset of complete arrest appeared in 36 (80%) of the 45 instances in which the patient died but in none of those who survived. Signs of cardiorespiratory difficulty were fluctuations of blood pressure and respiratory rates—particularly hypotension and apnea—cyanosis or dark blood, and variations in pulse rate and arrhythmias. Special mention should be made of the commonest alteration in heart

Submitted for publication Aug. 9, 1958.

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rate presaging cardiac arrest—bradycardia—characteristically a slow bounding pulse (20 to 40 beats per minute).

Age and sex were not of significance. In two cases dark skins were considered to have interfered with the early recognition of dusky cyanosis. Of the 38 different surgical procedures, major and minor, no single operation had a predilection for arrest. Arrest occurred before, at various intervals during, and after the surgical procedures were completed. Although overanesthetization was important in a majority of cases, no single agent or route could be indicated as the predominant cause.

Reversibility of Effects of Causes of Arrest

Reversibility of effects of causes of arrest was a most important factor, both in survival and in degree of recovery. In a number of instances, neurologic reflex mechanisms arose from stimulation of branches of the vagus nerve by surgical manipulation in the regions of the carotid sinus, styloid process, or stomach, by bronchial and esophageal irritation or by handling of the heart and great vessels. Half of these patients recovered completely; additional major complications were present in those who did not survive. As shown in Table 1, of the cases in which overanesthesia was present, 71% survived; approximately half of the patients survived when the airway was blocked by bronchial secretions. In striking contrast, when the airway was blocked by aspirated vomitus, none survived.

Airway obstruction, while certainly not synonymous with decreased blood volume, is similar to it in that when either has progressed to the point where its effects are irreversible, the patient dies. Impairment of cardiac function and decreased pulmonary function also are causative factors whose effect was seldom overcome.

Major Complicating Causes of Cardiac Arrest Whose Effects May Be Irreversible

The importance of complicating causative factors is highlighted by their presence in 44 of the 45 cases with fatal outcome in the four-minute group; 17 had one, 21 had two, and 7 had three major complications. In Table 2, the relationship of decreased pulmonary function, reduced blood volume, and impaired cardiac function to the degree of recovery is indicated.

Persons Who Survived.—None of the persons who survived had impaired cardiac function and pulmonary complications were confined to mild emphysema and induced pneumothorax. Decreases in blood volume were minimal—preexisting anemia, one case; and hemorrhage, two cases.

Persons Making Cardiac Recovery.—Three patients in this group were in congestive heart failure, and three had suffered recent unsuspected myocardial infarctions. Other complications were tamponade, one case; massive fatty necrosis and traumatic rupture, one case each, and advanced arteriosclerotic heart disease, one case. In four instances patients were in shock at the start of surgery: in two, the shock was secondary

TABLE 1.—*Survival as Related to Reversibility of Effects* *

	Overanesthesia (41 Cases)	Bronchial Obstruction, Secretions (13 Cases)	Aspirated Vomitus (4 Cases)
Survived	29 (71%)	6 (46%)	-------
Died	12 (29%)	7 (54%)	4 (100%)

* Complete cardiac and cerebral recovery of function may be achieved by prompt resuscitation (within 4 min.) when the effects of the causative factors are reversible.

TABLE 2.—*Relationship of Major Complicating Causative Factors to Degree of Recovery* *

	Decreased Pulmonary Function (20 Cases)	Reduced Blood Vol. (22 Cases)	Impaired Cardiac Function (20 Cases)
Survived	2 (mild) 10%	3 (mild) 14%	-------
Died	18 90%	19 86%	20 (100%)

* Prompt resuscitation (within four minutes) may not result in cardiac and cerebral recovery when the effects of severe complicating factors are irreversible.

to ruptured peptic ulcer; in an additional two, shock followed ruptured bladder and multiple fractures (one case) and intestinal obstruction (one case). Massive hemorrhage was present in four cases. Causes of pulmonary functional impairment included pneumonia (three cases), pulmonary effusion (one case), hemothorax (one case), and massive bilateral pulmonary emboli (one case). Other complications were single instances of dissecting abdominal aneurysm, pyelonephritis, acute hepatic necrosis, and meningitis with a dural thrombus.

Persons Making Neither Cardiac Nor Cerebral Recovery. — Factors impairing cardiovascular function predominated in this group. They include heart failure (three cases); two cases each of rupture of ventricular wall secondary to cardiac compression, tricuspid atresia, tetralogy of Fallot, and irreparable atrial septal defect, and one case each of endocardial fibroelastosis, cor pulmonale, recent unsuspected myocardial infarction, and cardiac tamponade.

Pulmonary complications included cavitation and fibrosis due to advanced tuberculosis (three cases), atelectasis (two cases), bronchiectasis (three cases), pneumonia (three cases), emphysematous blebs and cystic disease (two cases), pulmonary infarction and hemothorax (one case each).

Other complications were shock secondary to ruptured abdominal viscus or mechanical obstruction (three cases), uncontrollable massive hemorrhage (nine cases), and cocaine reaction (one case). Sudden change of position of the patient on the table from supine to right lateral was believed to be responsible for cardiac arrest in one case. There were two cases with intracranial pathology which could have decreased the resistance of the cerebrum to hypoxia.

Comment

As there is a four-minute limit for cardiac resuscitation at best, and the degree of cardiac and cerebral recovery is dependent on the time factor, it is essential that an accurate count be kept of the minutes that pass. In the crisis of cardiac arrest, the internist is in an excellent position to note the exact time of arrest and announce the termination of each minute while the anesthesiologist makes sure of an open airway and proper oxygenation and the surgeon makes ready for thoracotomy for manual compression.

As monitor of the electrocardiograph or cardioscope, the internist may be the first to note arrhythmias—particularly the bradycardia, which is a premonitory sign of cardiorespiratory embarrassment and of impending cardiac arrest. While the electrocardiogram adequately demonstrates ventricular fibrillation, it cannot be relied upon to diagnose ventricular asystole, because good QRS complexes still may be obtained, even though the ventricles have been in complete standstill for over five minutes.[6]

In the preoperative preparation of the patient, the internist should assume responsibility for those prophylactic measures which must be taken if the irreversibility of the effects from major complicating factors are to be minimized: detection and adequate treatment of conditions causing decreased pulmonary function, hypovolemia, and impaired cardiac function.

Most diseases which produce decreased cardiorespiratory function can be detected through history, physical examination, and fluoroscopic and x-ray study of the heart and lungs. In the occasional case, additional studies may be necessary.

If impairment of pulmonary function is suspected, ventilation measurements from spirogram tracings, determination of the degree of bronchospasm, and arterial blood oxygen studies are useful in evaluating the degree of pulmonary function impairment and estimating the risk of anesthesia and surgery.[6] During the preoperative period the condition of the patient with chronic lung disease may be much improved by the use of intermittent positive-pressure breathing in emphysema, bronchodilators for bronchospasm, and antibiotics for infectious processes.[7] Hypercapnia as a cause of cardiac arrest may be averted by the adequate

elimination of CO_2 through the use of intermittent positive-pressure breathing.[8]

The internist should ascertain that the blood volume is within normal limits prior to surgery, for hypotension and hypoxia occur more quickly and more often and are much more difficult to regulate in patients undergoing major surgery in whom adequate blood volume has not been restored prior to operation. Decrease in blood volume is suggested by history of anemia, hemorrhages or weight loss, prolonged fever and vomiting, obvious pallor, or malnutrition and may be uncovered by the standard determinations for red blood cells, hemoglobin, and hematocrit. In patients with carcinoma in whom the history and laboratory tests are inconclusive, Hinchey[9] suggests determination of blood volume by the Evans dye test or isotope dilution techniques, for significant reduction in blood volume still may be present.

Preoperative electrocardiographic studies are important in detection of recent unsuspected or silent myocardial infarctions—present in four of the cases with fatal outcome. Determination of the serum transaminase levels would be a helpful adjunct, in the absence of trauma to skeletal muscle and hepatic insufficiency.

Diagnosis and proper management of heart failure and cardiac tamponade should be done in the preoperative period to bring the patient to surgery in the best possible condition. Uncorrected congestive heart failure was present in six and tamponade in two of the cases with fatal outcome.

In addition to digitalizing hearts in failure and treating arrhythmias, the internist should see to it that fluids and electrolytes are balanced and blood chemistry is in good order. Immediate surgery rarely is necessary, except for respiratory obstruction or hemorrhage; prompt surgery can be delayed unless the circulation has been compromised.

The fatal outcome in all of the four cases in which vomitus was aspirated emphasize the danger of vomiting during or immediately after anesthesia. If there is not at least five hours following ingestion of food, the patient's stomach should be lavaged or preferably emptied by induced vomiting. Emotion and apprehension can delay gastric emptying and "the markedly apprehensive patient is a potential candidate for death in the operating room."[10] The mechanism of death due to apprehension is obscure; it was considered a contributing factor in one of the cases of this series. Apprehension may be counteracted by reassurance, thorough discussion, and by judicious preoperative sedation.

From his knowledge of the patient's response to previous medications, the internist can forestall anesthetic difficulties and sensitivity reactions. Three instances of reactions to cocaine derivatives occurred in this series. In addition, the internist should adjust the patient's usual daily medications to meet the stress and strain of surgery. Cortisone should be maintained or increased before and after operation.[11] Persons receiving reserpine should be watched to prevent hypotensive reactions during and for 10 days following surgery.[12] Allowance should be made for the ganglionic blocking agents and anticoagulants which may be given preoperatively.[13] Eckenhoff[10] found the blood pressures of several anesthetized patients previously treated with chlorpromazine dropped precipitously when their body position was changed on the operating table.

During arrest and in the postresuscitation period, the internist should be ready to advise proper administration of drugs to restore the heart beat. The most effective drug in standstill is epinephrine, 1 to 2 cc. of a 1:1,000 solution diluted with 9 cc. of isotonic saline, injected into the cavity of the left ventricle.[14] Small repeated doses should be used, as a single large dose may cause ventricular fibrillation. When epinephrine has failed, 2 to 4 cc. of a 10% solution of calcium chloride has succeeded.[15] It is beyond the scope of this paper to discuss the use of all drugs in cardiac arrest, except to say that Hosler[16] has set up an emergency drug tray for the operating and recovery rooms, containing atropine, lanatoside D,

caffeine, levarterenol, (*l*-norepinephrine) mephentermine, quinidine, calcium chloride, and potassium chloride.

While, medicolegally, only the surgeon may consider himself responsible, anesthesiologists have done emergency thoracotomies.[17] The cardiologist member of a catheterization team recently had to perform a thoracotomy to resuscitate successfully an arrested heart.[18] Should the emergency arise in the hospital, the consultant cardiologist and the internist who accompanies his patient to the operating room should be prepared properly and promptly to resuscitate a heart in arrest.

Outside the hospital, the internist contemplating thoracotomy should bear in mind that (as in this series of cases) in the presence of hypovolemia and impaired cardiopulmonary function, and if arrest has existed longer than four minutes, complete recovery is unlikely, and partial success may result in a decerebrate person. The eight persons in our series with permanent damage to the central nervous system from incomplete recovery from cardiac arrest represent an estimated annual incidence of 100 persons who have recovered only enough to spend the remainder of their lives in institutions for custodial care.

The internist is going to meet with cardiac arrest in the course of coronary artery disease and as a common mechanism in Stokes-Adams attacks; less frequently in drowning, electrocution, and as a toxic reaction to digitalis, quinidine, and procaine amide.[19] In these situations the internist should not attempt thoracotomy unless there is a surgeon readily available to stop the "spurters" when the heart resumes its beat and an anesthesiologist to insure oxygenation through an adequate airway.[20] Hosler [16] says the thorax should not be entered without a positive-pressure apparatus.

Zoll [21] has accomplished resuscitation of patients from ventricular standstill and fibrillation with a countershock electric current applied externally to the closed chest. The internist should be able to apply external electric stimulation and external electric defibrillation for unexpected cardiac arrest and for the recurrences during the first two or three days of the postresuscitation period.

Summary

The chief cause of high mortality in 132 cases of cardiac arrest was delay of more than four minutes between onset of arrest and start of treatment. The internist may shorten this interval by continuously monitoring the cardiographic tracing to detect the first sign of cardiorespiratory embarrassment, usually bradycardia or arrhythmia, in time to warn the surgeon and anesthesiologist so that action can be taken to prevent impending arrest. From the instant of onset, the internist should announce the passage of each minute until thoracotomy and cardiac compression have begun.

When prompt resuscitation failed (within four minutes) major complicating factors were present. The internist acts to prevent cardiac arrest by detection and adequate treatment of conditions causing decreased pulmonary function, hypovolemia, and impaired cardiac function in the preoperative period before their effects can cause irreversible cardiac arrest. He must adjust the patient's habitual medication with reserpine, chlorpromazine, anticoagulants, insulin, or corticosteroids to meet the requirements of anesthesia and surgery.

The internist must be able to advise the surgeon and anesthesiologist as to the proper administration of drugs to restore the heartbeat. In the postresuscitation period, he should observe the patient to detect and treat conditions interfering with recovery and to assess the final amount of impairment of the central nervous system.

The cardiologist on the catheterization team and the internist who accompanies his patient to the operating room should be trained and prepared to resuscitate promptly and properly an arrested heart. For the present, the internist should not attempt thoracotomy where surgeons and anesthesiologists are not readily available; he may

apply electric countershock currents externally to the closed chest.

The financial assistance of The Beneficial Standard Life Insurance Company, Spiros Ponty, Charles P. Skouras and Wallis Foundations and Messrs. and Mmes. E. Cantor, Irving Feintech, Norman Feintech, William Forman, E. Mitchell, William Wilkerson and Dr. and Mrs. Jules Stein made this study possible.

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Personality Factors and Pressor Mechanisms in Renal and Essential Hypertension

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Studies of the personalities of patients with "essential" hypertension conducted by several independent observers have exhibited some agreement.[1-11] "What emerges from these studies is evidence of certain kinds of conflictive situations which these patients seem unable to resolve. By and large, they cannot accept either their strong passive dependent attitudes or freely express their hostile impulses." [12] Gressel [13] observed a statistically significant association of hypertension with "obsessive-compulsive behavior" and with "subnormal assertiveness."

The evidence that psychological factors are etiologically related to "essential" hypertension has rested on the following observations:

1. Blood pressure commonly rises in hypertensive subjects during threatening events either occurring in life or contrived in the laboratory.

2. Blood pressure in hypertensive subjects commonly falls during sleep or after relaxation or reassurance.

3. Some investigators claim that there is a predictable association of certain specific intrapsychic conflicts or personality traits with elevated blood pressure.

In order to examine the relevance of psychological factors to essential hypertension, the best control group, we believe, is not a group of normotensives or subjects with another "psychosomatic" disorder but a group of patients with hypertension of renal origin. It is necessary in the latter group to establish that major primary renal disease existed and that it antedated the elevation of blood pressure. Furthermore, the subjects with essential hypertension and with renal hypertension should be similar in age, sex, race, education, and socioeconomic status. None should be studied because of associated psychiatric disorders, verbal facility, or desire to enter psychotherapy, since inclusion of such patients would bias the group performance. Finally, the measures utilized to assess psychological factors and life stress should be predetermined, standard, and susceptible of statistical handling. The present study was undertaken to examine the relevance of personality, behavior, and psychological stress to elevated blood pressure while the above specifications in experimental design were met.

Should psychological factors underlie essential hypertension in the same way that disordered renal function presumably underlies renal hypertension, differences in blood pressure responses to stress, in the mechanism of such rises, and in personality structure ought to be apparent in the two groups. The present study was initiated to examine for such differences and to illuminate the relationship of psychological factors to the etiology of essential hypertension.

Method

Two groups of subjects were examined. Those with essential hypertension ranged in age from 28 to 48, with a mean of 39.0. Sixteen were women; two, men. The renal hypertensives ranged from 21 to 61, with a mean age of 40.6. Twelve were women; three, men. Patients were obtained from the admitting clinic, wards, and medical clinics of the University of Illinois Research and Educational

Submitted for publication Oct. 9, 1958.

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TABLE 1.—*Subjects with Essential Hypertension*

No.	Age	Sex	Fundi *	Representative Urine				N. P. N.	Intravenous Pyelogram
				Sp. Gr.	Alb.	Microscopic Examination	Culture		
1	28	F	II	1.017	1+	Neg.	Sterile	30	Normal
2	38	M	II	1.018	0	Rare WBC	Sterile	21	Normal
3	49	F	I	1.027	0	Neg.	Sterile	25	—
4	40	F	I	1.023	0	Neg.	Sterile	22	Normal
5	39	M	II	1.016	Tr.	Neg.	—	15	Normal
6	37	F	II	1.017	0	2-3 WBC	Sterile	28	Normal
7	39	F	IV	1.014	3+	2-3 WBC, occ. gran. cast	Sterile	26	Normal
8	35	F	I	1.023	0	Rare hyal. cast	Sterile	26	—
9	44	F	III-IV	1.016	0	Occ. hyal. & finely gran. cast	—	22	Normal
10	48	F	I	1.022	0	1-2 WBC	Sterile	18	—
11	42	F	I	1.024	0	Neg.	—	19	Normal
12	40	F	III	1.012	Tr.	Occ. hyal. cast	Few micrococci $<10^3$	33	Normal
13	45	F	II	1.017	0	Neg.	—	26	Normal
14	43	F	II	1.021	Tr.	Rare WBC, rare RBC	—	32	Normal
15	28	F	I	1.026	0	Neg.	—	22	—
16	41	F	II	1.023	Tr.	Occ. gran. cast	Sterile	24	Normal
17	36	F	II	1.020	0	Rare hyal. cast	Sterile	29	—
18	30	F	I	1.024	0	Neg.	Sterile	21	—

* Keith-Wagener classification.

Hospitals and the Cook County Hospital. Medical records at these institutions and hospitals, which the patients attended earlier, were examined to aid in determining the validity of the diagnosis of renal or essential hypertension. The diagnosis of renal or essential hypertension was based upon the natural history of the disorder, repeated urinary sediment examinations, urine cultures, and intravenous pyelograms. In 8 of the 15 renal hypertensives the diagnosis was supported by renal biopsy or necropsy (Tables 1 and 2). The "essential" group was limted to those free of urinary tract infection, and the subjects with pyelonephritis included in the "renal" group were limited to those in whom chronic infection antedated the onset of hypertension. The single post-toxemic subject included in the "renal" group was normotensive until the development of eclampsia and has remained hypertensive since then.

All subjects were southern-born Negroes, who had been residing in Chicago for from 3 to 26 years. For both groups the mean educational level was ninth grade. Approximately 90% of both groups were or are married (usually a common-law marriage). Two-thirds of the "essential" group and one-half of the "renal" group were employed during or immediately before the period of study. The women were employed as domestics, laundry workers, semiskilled laborers, or beauty parlor operators; the men, as unskilled or semiskilled factory workers. The subjects with renal hypertension were as a group more ill and uncomfortable in a bodily sense.

All the physiological assessments and, with a single exception, all the psychological testing was carried out in the absence of antihypertensive therapy or dietary restriction. Studies were begun after the subjects were familiar with one investigator and after all had been in attendance at the clinics for at least three visits or in the hospital for at least one week.

After the usual medical work-up, the physiological and psychological assessments were made. The latter tests were administered once only during a period of relative tranquility in the lives of the subjects; the former, once during a period of tranquility and again during a period of agitated behavior in the subjects' lives. A tranquil period was one during which no events perceived by the patients as threatening had occurred and when the patients' speech content and behavior were compatible with tranquility. A period of agitation was one during which a single unusually threatening event had occurred and the patient's verbalization, associations, and behavior were compatible with their perception that the event was highly threatening. The feeling state, reported by the subjects and observed by us, was predominantly anxiety and on two occasions fear. Typical of the threatening events were the following: One subject was studied while her husband was in hepatic coma; another, while her child was undergoing eye surgery; a third, immediately after she had been awakened at 5 a. m. and questioned by police for three hours about a neighbor's death. We deliberately waited sometimes as long as eight months for such an event to occur, in order to make the appropriate measurements. The longest interval between the "tranquil" and "agitated" measurements was nine weeks.

Two psychological tests were administered: the Minnesota Multiphasic Personality Inventory

TABLE 2.—*Subjects with Renal Hypertension*

No.	Age	Sex	Fundi	Representative Urine *				N. P. N.	Intravenous Pyelogram	Tissue Diagnosis	Clinical Diagnosis
				Sp. Gr.	Alb.	Microscopic	Culture				
1	21	F	II	1.012	3+	0-2 WBC, occ. gran. cast	Proteus vulgaris	50	—	Biopsy: membranous glomerulonephritis Autopsy: chronic glomerulonephritis	Chronic glomerulonephritis
22	36	M	III-IV	1.014	2+	2-5 WBC, occ. hyal. & gran. cast	Sterile	73	Poor visualization otherwise normal	Biopsy: membranous glomerulonephritis	Chronic glomerulonephritis
3	46	F	III	1.020	2+	Occ. hyal. cast	Sterile	27	Normal	—	Post-toxemic hypertension
4	61	F	II	1.012	2+	5-6 WBC, occ. hyal. & gran. cast	Escherichia coli. micrococci	88	—	Autopsy: chronic pyelonephritis	Chronic pyelonephritis
5	53	F	III	1.013	2+	10-12 WBC, occ. hyal. & gran. cast	Aerobacter aerogenes; proteus rettgeri	62	—	—	Chronic pyelonephritis
6	42	M	I	1.020	4+	Many RBC & NBC casts	Sterile	70	Poor visualization otherwise normal	Biopsy: acute exudative & proliferative glomerulonephritis	Subacute glomerulonephritis
7	46	F	III	1.010	1+	3-4 WBC, few gran. casts	E. coli	25	Compatible * with pyeloneph.	—	Chnronic pyelonephritis
8	38	F	II	1.013	3+	8-12 RBC, 1-4 WBC, many hyal. casts	Micrococci	70	Normal (previous film)	Biopsy: membranous glomerulonephritis	Chronic glomerulonephritis
9	37	F	Micro-aneurysms	1.012	3+	Few hyal. & gran. casts rare WBC	Sterile	28	—	Biopsy: Kimmelstiel-Wilson lesion	Diabetic nephropathy
10	41	F	II	1.001	1+	Occ. WBC	E. coli.	30	Compatible * with pyeloneph.	—	Chronic pyelonephritis
11	46	F	I	1.007	Tr.	Occ. WBC many gran. casts	Gamma strep.	44	Compatible * with pyelo.	Surgical specimen: acute & chronic pyelonephritis	Chronic pyelonephritis
12	20	M	II Micro-aneurysms	1.020	4+	Occ. WBC, oval fat bodies	Sterile	45	—	Biopsy: Kimmelstiel-Wilson lesion	Diabetic nephropathy
13	45	F	II	1.016	Tr.	1-4 WBC, occ. gran. casts	E. coli; A. aerogenes	27	Compatible * with pyelo.	—	Chronic pyelonephritis
14	38	F	I	1.012	1+	6-8 WBC, mod. no. gran. casts	Pseudomonas aelruginosa	34	Compatible * with pyelo.	—	Chronic pyelonephritis
15	41	F	II	1.019	1+	4-6 WBC, occ. hyal. & gran. cast	Proteus mirabilis	66	—	—	Chronic pyelonephritis

* Exhibiting calyceal distortion, dilatation, and/or blunting.

(MMPI) and the Rorschach. The former is a true-false questionnaire, which assesses the degree to which certain kinds of clinical psychopathology are present. It was utilized because it is machine-scored, independent of observer bias, and susceptible of statistical handling. The latter, the well-known ink-blot test, is a projective technique which elicits a different kind of psychopathology than the MMPI, assesses unconscious attitudes and motivation, and permits observer judgements.

All 18 subjects with "essential" hypertension and 15 with presumed "renal" hypertension completed the MMPI. In addition, 18 normotensive subjects, matched with "essentials" for age, sex, race, education, employment, and marital status, also completed the MMPI. These subjects came from gynecology, surgery, and general medical clinics. In the case of the Rorschach, however, only 10 "renal" subjects and 16 "essential" subjects completed the test. Retinopathy with visual impairment made interpretation of the ink blots too difficult for 7 of the 33 subjects.

The Rorschachs were scored and rescored for reliability, with the minimum reliability being in the 80's for form level. A comparison of the responses of the "renals" and "essentials" was made according to the De Vos content analysis[14] and according to Thaler's modification of the De Vos analysis.[15] The renal hypertensives, essential hypertensives, and normotensive subjects were compared on the MMPI for the mean scores on the separate scales, for the patterning of the scales, and for the significance of the separate scale items.

Three physiological measurements were made on the subjects during tranquility and during disturbed behavior. If one set of measurement was made while the patient was in the hospital, the other was likewise made while the subject was hospitalized. Similarly, if one set of measurements was made in the OPD, the second set was made under the same circumstances. The physiological assessments were as follows:

1. Blood pressure was measured after 10 minutes in the supine position.

2. Four hundred milligrams of tetraethylammonium chloride (TEAC) was administered intravenously rapidly and its effect on supine blood pressure measured according to the technique of Brust and Ferris.[16] The blood pressure effects of TEAC were called "pressor," "no response," or "depressor," according to the criteria of these authors. This technique had been utilized by Ferris and associates in studying humoral and neural control of blood pressure in renal disease,[16] in toxemia of pregnancy,[17] and during period of reduced salt intake.[18]

3. The responsiveness of the bulbar conjunctival minute vessels to topical levarterenol (*l*-norepinephrine) was assayed. This technique was employed because Lee had shown that the bulbar conjunctival vessel responsiveness to topical epinephrine was greatly increased during a paroxysm of elevated blood pressure in phenochromocytoma.[19] The method used was that of Lee[20] except that levarterenol was employed instead of epinephrine. The threshold was defined as the least concentration of topically applied levarterenol which blanced conjunctival capillary beds (Figure).

Results

Pertinent medical data on each group are included in Tables 1 and 2.

The results on the MMPI are as follows:

Mean Scores.—Table 3 lists the mean *t*-scores for the separate scales. The dif-

The photo at the left shows some arterioles, venules, and capillaries of the bulbar conjunctivae of a hypertensive subject in their usual state. At the right, 1:200,000 topical levarterenol has been applied. Capillaries are no longer visible; the arterioles and venules are narrowed, and the venular blood has a granular "sludged" appearance.

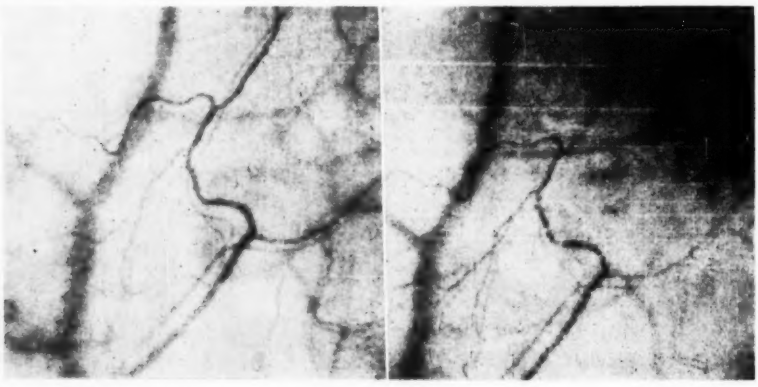

TABLE 3.—*Mean t-Scores of the MMPI Scales*

	Renals	Controls	Essentials
k (defensiveness)	55.6	51.3	51.9
Hypochondriasis	63.3	63.3	61.3
k-corrected	67.9	65.2	63.4
Depression	67.5	65.3	67.8
Hysteria	66.8	64.5	66.5
Psychopathic deviate	64.5	64.5	64.7
k-corrected	66.1	63.9	64.8
Paranoia	57.9	61.6	57.8
Psychasthenia	53.3	55.7	55.8
k-corrected	59.7	58.9	59.3
Schizophrenia	54.3	59.6	55.7
k-corrected	61.2	63.8	59.0
Hypomania	52.6	56.6	58.6
k-corrected	53.3	56.4	59.1
N	15	18	18

ferences were evaluated by the χ^2 median test, correcting for one degree of freedom. None of the differences are significant, and no trends seem apparent. The three groups are similar in the average scores on the separate scales.

Pattern Analysis.—The eight clinical scales, excluding the MF scale, were ranked for each person. These rankings were then summed and a mean group rank for the eight scales determined. Table 4 presents the mean ranks, based upon the uncorrected scores, and Table 5, the scores corrected for *k*. (The *k*-score is used to sharpen the discriminatory powers of the test by correcting for tendency to distort answers in the direction of a more "normal" appearance.) When the ranks are evaluated by the χ^2 median test, corrected for one degree of freedom, no significant differences are found.

Item Analysis.—The 566 items on the MMPI were examined for each of the two

TABLE 5.—*Comparison of the Mean Ranks of the Eight Clinical Scales—k-Corrected*

	Renals	Controls	Essentials
Hypochondriasis	3.3	3.98	4.08
Depression	3.2	3.85	3.28
Hysteria	3.07	3.90	3.70
Psychopathic deviate	3.57	3.8	3.98
Paranoia	5.3	4.8	5.2
Psychasthenia	5.8	5.4	5.4
Schizophrenia	5.13	4.38	5.3
Hypomania	6.56	5.83	5.05

TABLE 4.—*Comparison of the Mean Ranks of the Eight Clinical Scales—k-Uncorrected*

	Renals	Controls	Essentials
Hypochondriasis	3.60	4.03	4.55
Depression	2.83	3.63	3.00
Hysteria	2.90	4.03	3.78
Psychopathic deviate	3.60	3.78	3.78
Paranoia	4.83	4.50	4.65
Psychasthenia	6.40	5.68	5.45
Schizophrenia	6.00	4.95	5.45
Hypomania	5.87	5.43	5.28

groups. A comparison was first drawn between the number of persons answering "true" on the items in the hypertensive and renal groups. Table 6 lists the items that were answered significantly differently by the two groups at the 5% level or better, with use of the χ^2 median test corrected for one degree of freedom. With the exception of Item 165, the hypertensive groups answered "true" more frequently than the "renal" group. On Item 165, the "renal" group answered true more frequently. However, by chance alone, one would expect *some* items of the 566 to show a level of significance at even the 0.005 level, the most significant item of the eight.

The Rorschach.—The scores on the De Vos method of content analysis are found in Table 7. The only significant difference found is in regard to anxiety. The "renal" subjects are significantly more anxious (P 0.001), when the differences are based upon the total number of subclasses listed by De Vos and evaluated by means of

TABLE 6.—*Items on the MMPI to Differentiate the Renal and Hypertensive Groups*

Item No.	
5	I am easily awakened by noise ($P<0.005$)
112	I frequently find it necessary to stand up for what I think is right ($P<0.05$)
134	At times my thoughts have raced ahead faster than I could speak them ($P<0.02$)
165	I like to know some important people because it makes me feel important ($P<0.05$)
465	I have several times had a change of heart about my life work ($P<0.01$)
547	I like parties and socials ($P<0.05$)
549	I shrink from facing a crisis or difficulty ($P<0.02$)
566	I like movie love scenes ($P<0.02$)

TABLE 7.—*Scores on the Rorschachs Evaluated By the De Vos Method*

	Renals		Essentials	
	0	1	0	1
All categories				
Anxiety	0	10	0	16
Hostility	7	3	8	8
Body concern	4	6	5	11
Using Thaler's grouping				
Anxiety	7	3	6	10
Hostility	9	1	12	4

the χ^2 median test corrected for one degree of freedom. With use of Thaler's categories alone, 25% of the group of essential hypertensives show "hostility" and 40% show anxiety. Thaler's figures for these respective categories are 80% and 27%.

The measurements made during tranquil and agitated periods are shown in Tables 8 and 9 for the two groups. There was a significantly higher blood pressure both systolic ($P<0.001$) and diastolic

TABLE 8.—*Essential Group*

	Tranquil			Agitated		
No.	B. P.	Eye	TEAC Response	B. P.	Eye	TEAC Response
1	172/110	1:200,000	Depressor	188/120	1:200,000	Pressor
2	158/110	1:200,000	Depressor	165/110	1:400,000	Pressor
3	174/112	—	Depressor	174/110	—	Depressor
4	138/98	1:200,000	No response	158/114	1:800,000	Pressor
5	210/130	1:200,000	Depressor	220/136	1:400,000	Depressor
6	170/112	1:100,000	Depressor	166/110	1:100,000	Depressor
7	220/134	—	—	238/146	—	—
8	144/96	1:100,000	Depressor	160/104	1:400,000	No response
9	190/116	—	—	220/132	—	—
10	162/98	1:200,000	Depressor	180/108	1:400,000	Depressor
11	152/100	—	Depressor	166/110	—	Depressor
12	176/128	1:200,000	Depressor	208/144	1:800,000	Depressor
13	182/130	1:400,000	Depressor	182/130	1:400,000	Pressor
14	172/104	1:200,000	Depressor	216/130	1:400,000	Pressor
15	144/100	1:100,000	Depressor	150/112	1:400,000	Depressor
16	192/122	1:100,000	Depressor	204/128	1:100,000	Depressor
17	142/98	—	—	154/112	—	—
18	172/110	1:400,000	Depressor	182/114	1:800,000	Pressor

TABLE 9.—*Renal Group*

	Tranquil			Agitated		
No.	B. P.	Eye	TEAC Response	B. P.	Eye	TEAC Response
1	138/100	1:200,000	—	150/106	1:800,000	—
2	200/120	—	—	200/122	—	—
3	208/132	1:200,000	Depressor	224/144	1:400,000	Pressor
4	178/94	1:200,000	Depressor	244/126	1:400,000	Depressor
5	230/130	1:400,000	Depressor	248/136	1:800,000	Depressor
6	144/92	—	No response	150/104	—	Pressor
7	202/118	1:100,000	Depressor	230/134	1:400,000	No response
8	160/110	—	Depressor	165/115	—	Pressor
9 *	—	—	—	—	—	—
10	155/105	1:200,000	Depressor	235/115	1:800,000	Depressor
11	160/108	1:400,000	Depressor	178/120	1:400,000	Depressor
12	210/130	—	Depressor	205/130	—	Depressor
13	212/124	1:400,000	Depressor	226/130	1:800,000	Pressor
14	164/108	1:100,000	Depressor	170/100	1:200,000	Depressor
15	182/114	1:200,000	Depressor	No period of agitated behavior was observed.		

* This subject was receiving antihypertensive treatment during the period of study.

($P<0.001$) in the "essential" group during stress as compared to tranquility. The same relationship was true for the "renal" group for both systolic ($P<0.05$) and diastolic ($P<0.01$) readings. Moreover, the percentage increase in systolic and diastolic pressures during agitation was similar in both groups, there being no significant difference.

There was a significant decrease in levarterenol threshold for both groups during the period of agitation ($P<0.05$), with the decrease being of roughly the same magnitude in both groups. Finally, there was a tendency toward reversal of the usual depressor effect of TEAC during stressful periods in 7 of the 15 "essentials" so studied and in 5 of the 11 "renals" tested.

Comment

The psychological test score patterns of the "renals" and "essentials" were very similar with respect to the MMPI whether attention was centered on the individual scales or the relative positions of the clinical scales within their rankings. The only differences that were found involve single items which are not on any of the clinical scales and do not appear to represent specific attitudes or personality configurations. Repressed aggression has been postulated by some to underlie the elevated blood pressure in essential hypertension. Since repressed aggression according to psychiatric theory often manifests as depression, it is interesting to examine the scores of the three patient groups on the Depression Scale of the MMPI. There is no difference in this score in the three groups.

On the Rorschach test as well, there was an equal percentage of hostile responses from the two groups. The percentage of hostile responses was far smaller than that reported, in a group of male hypertensive subjects in an Armed Forces hospital, by Thaler [15]. She found that hypertensive subjects gave many hostile responses and saw the patient-physician relationship as threatening, as compared to a group of peptic ulcer patients who viewed the physician as a helpful, nonthreatening figure. In this connection, it must be remembered that ulcer patients consult physicians because they have a pain in the abdomen and the doctor's diet and medicines usually relieve the pain. Hypertensives often have no symptoms and are referred to hospitals because a blood pressure reading is found to be high. They have no complaint which the doctor can alleviate, and antihypertensive medication is notorious for its undesirable side-effects. Differences in attitude toward the physician may be related to differences in the above factors rather than to the personality of the patients.

The somewhat larger number of anxiety responses among the "renals" may be related to the fact that most of them were hospitalized and were azotemic and seriously ill while they were being studied.

The decrease in levarterenol threshold and trend toward reversal of the usual depressor effect of TEAC are compatible topical epinephrine has been observed during a paroxysm of hypertension in a with an increase in a circulating vasoconstrictor agent. Increased responsiveness to patient with pheochromocytoma [19] and during toxemia of pregnancy.[21] Infusion of levarterenol has been shown to constrict nailfold vessels [22] and to lower the levarterenol thresholds of bulbar conjunctival vessels.[23] Reversal of the usual depressor effect of TEAC during psychological stress had been observed by Ferris [24] and by Hoobler, Moe and Lyons.[25] Wilber and Brust [26] have recently studied the mechanism of this reversal. They showed that TEAC potentiated the pressor effect of levarterenol but not epinephrine and that such potentiation was associated with an increase in pulse rate and cardiac output. It appears that in both renal and essential hypertension the moment-to-moment level of blood pressure is in part determined by humoral vasoconstrictor agents with prop-

erties resembling levarterenol more than epinephrine, whose levels are increased during periods of anxiety.

In both groups, when a major threatening event occurred and anxiety or fear was prominent, blood pressure elevations predictably occurred. No specific personality factors were demonstrable, nor were there any psychological processes, either consciously expressed on the MMPI or unconsciously projected on the Rorschach, which distinguished between the two groups. The similarity in age, sex, race, education, and socioeconomic status and the method of selection of the subjects may underlie the absence of psychological difference and indicates the need for such controls.

On the basis of these data, we postulate the following epidemiologic implications for essential hypertension. Psychological stress may be etiologically related to momentary levels of blood pressure. The effects of such stress summate with a "renal" factor in renal hypertension and an unknown factor(s) in essential hypertension. In renal hypertension, psychologic factors may raise blood pressure above its usual level but are not directly related to maintaining the elevation permanently. The striking parallelism between renal and essential hypertension observed in this study makes it likely that a similar relationship exists for essential hypertension; i. e., psychological stress may induce fluctuations in blood pressure, but is not etiologically responsible for the permanent elevation.

Other studies now being completed indicate that lability of blood pressure in hypertensive and normotensive populations is related significantly and positively to the presence of certain "neurotic" character traits. Severity of the disease, on the other hand, is not correlated with such psychological factors.

It may be that in certain "neurotic" subjects, the contribution of psychologically triggered mechanisms to blood pressure is very large, whereas in other "non-neurotic" patients, such mechanisms are of little importance to the elevation of the blood pressure. The presence or absence of the neurotic traits would be related to a number of genetic and environmental factors.

Some authors have postulated that repetitive blood pressure elevations induced by psychological stress eventuate in a permanent elevation of blood pressure. The studies, of Levy, White, Stroud and Hillman, in army officers are commonly quoted.[27] If, as Pickering's studies seem to show,[28] blood pressure increases with age, the data of Levy, White, Stroud, and Hillman need not be interpreted as these authors have chosen to do. Much of what is called essential hypertension may represent only psychologically induced pressor effects, superimposed on the expected rise in blood pressure with age. The "vascular hyperreactor" at age 25, whose blood pressure goes up with psychological stress, may become the "fixed hypertensive" of age 45 not because of the irreversible effects of repetitive stress but because of a superimposition of an acute elevation during stress on a blood pressure whose basal level is higher because of weight gain, a thicker upper arm, and a less elastic aorta.

The authors recognize two limitations in the study: 1. Definitive proof of a renal hypertension mechanism is obtainable only in those subjects who have unilateral renal disease and are permanently normotensive after appropriate surgery. In none of our subjects is the evidence of renal hypertension so indisputable. 2. Only blood pressure responses during anxiety were studied. Other strong-feeling states, such as anger, did occur in both groups but not so frequently as anxiety. The fact that anxiety occurred more frequently than anger has been observed in most patient groups the authors have attended and is not postulated to be of significance here.

Summary and Conclusion

Two populations of hypertensive subjects, one presumably renal and the other

essential in origin, exhibited marked similarity in psychological test score patterns on the Rorschach and Minnesota Multiphasic Personality Inventory. Blood pressure responses to life stress and changes in vascular reactivity during such stress were likewise remarkably similar in the two groups. It is concluded that the role of psychological stress in renal and essential hypertension must be very similar and, therefore, that personality and attitudinal factors are not etiologically related to essential hypertension, serving only transiently to influence the level of blood pressure. The changes in vascular reactivity in both groups were so alike in magnitude and direction as to support the thesis that the same mechanism elevates blood pressure acutely during threatening situations in either renal or essential hypertension.

Dr. Robert M. Kark and associates gave us permission to study renal hypertensive Patient 9 and to examine the biopsy data obtained from renal hypertensive Patients 1, 2, 6, 8, and 9.

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The Bulbar Conjunctival Vessels in Occlusion of the Internal Carotid Artery

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The study of the reactions of the bulbar conjunctival vessels in man to physical and chemical stimuli has revealed vasoconstriction, vasodilatation, and alterations in the flow of blood cells. The appearance and behavior of these vessels in various clinical conditions have been described.

A constriction preceding and a dilatation of both large and minute conjunctival vessels during the migraine attack have been observed.[1-3] During the latter phases of pregnancy the capillary blood flow and the number of visible capillaries are often reduced.[4,5] In the eight to five days premenstrually, vasoconstriction and increase in spontaneous vasomotor activity in the capillary bed and tissue ischemia can be observed. At or just prior to the onset of menstruation there is arterial dilatation and a reduced velocity of blood flow.[6] Also, there are bulbar conjunctival vascular changes accompanying diabetes mellitus, arteriosclerosis (with and without renal impairment), and essential hypertension.[7,8]

The conjunctival circulation in disorders affecting the circulation of the internal carotid artery, however, has not been studied. Since the conjunctiva receives its blood supply from branches (dorsal, nasal, and lacrimal) of the ophthalmic artery, study of the bulbar conjunctival blood vessels makes possible the examination of the terminal part of a vascular tree whose origin is the same as that which supplies a large part of the cerebral hemisphere. Retinal artery pressures are significantly lower on the side of a thrombosed or surgically ligated internal carotid artery.[9-11] However, after ligation of the common carotid, probably because of a more adequate establishment of collateral circulation, the lowering of the retinal arterial pressure persists for a shorter time than with occlusion of an internal carotid artery.

During routine observations of the bulbar conjunctival blood vessels of patients with a variety of vascular diseases, differences in appearance of the vessels of the two eyes were noted in those having unilateral thrombosis of the internal carotid artery. Evidence of insufficiency of circulation in the central retinal artery, indicating thrombosis of the internal carotid artery, was clinically manifested in these patients by disturbances in vision, such as blurring and transient blindness, and by the low blood pressure (often less than half of the normal) in the retinal artery on the side of the occlusion. This suggested that impairment of the bulbar conjunctival circulation might be detected by examination of these blood vessels, since both retinal and uveal circulation are of common origin (from the ophthalmic artery), and the blood pressure normally is about the same in these two arterial systems of the eye.

Materials and Methods

Description of Subjects.—Included in these studies were 41 patients and 12 healthy adult subjects.

Submitted for publication Oct. 28, 1958.

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Supported in part by a research grant from the Society for the Investigation of Human Ecology and in part by a research grant from the National Institute of Health, U. S. Public Health Service, Bethesda, Md.

Five patients had thrombosis of the internal carotid artery, and one patient had thrombosis of the common carotid artery, all proven by arteriograms. Two of these patients had had right cervical sympathectomy performed after thrombosis of the right internal carotid artery. In one, the operation had preceded these studies by 25 days; in the other, by 3½ years. One patient had had a surgical ligation of the common carotid artery. Four patients, because of their signs and symptoms, were diagnosed * as having thrombosis of the internal artery, but arteriograms had not been made.

The observations made on these 11 patients with proven and suspected occlusion of the internal carotid artery were compared with those made on 30 patients with cerebral arteriosclerosis with or without hypertension and without occlusion of the internal or common carotid arteries. Five of these latter patients had had cerebrovascular accidents involving the middle cerebral artery, and two of them had thrombosis of the central retinal artery, with secondary atrophy of the optic nerve. One patient was examined a few days after a cerebral hemorrhage from a congenital arteriovenous anomaly of the deep branches of the middle cerebral artery. Another patient was examined after the establishment of an arteriovenous fistula (cavernous sinus-internal carotid artery) following trauma.

The systemic arterial blood pressures of the 11 patients showed no gross fluctuations during the entire period of the observation, and in no instance was it significantly different from that before the occlusion. None of them was in critical condition from general circulatory disturbances. Two patients exhibited slight arterial hypertension. One patient was reported to have been hypertensive in the past, but his blood pressure levels had been within the normal range for months before the examinations of the bulbar conjunctival vessels were made.

Method of Examination.—Examination of the bulbar conjunctival vessels was performed by means of an ophthalmic slit lamp of the Bausch and Lomb-Poser type. Magnification was × 60 and × 75. Examinations were repeated on several successive days and, for nearly all of the subjects, at subsequent intervals of one to two months for a period of nine months.

The caliber and color of the bulbar conjunctival vessels of both eyes in corresponding areas near the limbus and temporal intermediary zones were noted and compared. Photographs were taken of each eye in exactly corresponding areas through a camera adapted to the microscope. Equal intensities of illumination for each eye and the same magnification were used.

Differences in the velocity of the blood flow in arteries, veins, and minute vessels of the two eyes were estimated by timing the movement of the red blood corpuscles in each eye.

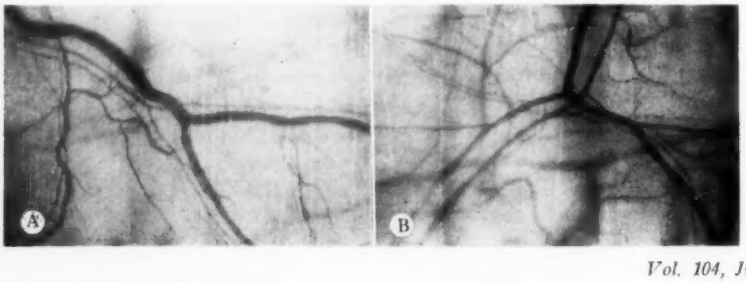
Results

Series I

Patients with Occlusion of Internal Carotid Artery Compared with Thirty Patients with Other Vascular Disease and Twelve Intact Subjects.—A. Dilatation of Arteries, Arterioles, Veins, and Venules, Paucity of Minute Vessels: On examination with the

* The criteria for diagnosis [10] were as follows: (1) Pain over and behind the eye and low in the temporal region on the side of the occlusion (Such headache is periodic, and the pain, steady rather than throbbing.); (2) transient monocular blindness on the same side of the occlusion; (3) transient numbness of an arm and/or a leg on the side opposite the occlusion; (4) transient or long-lasting aphasia; (5) transient disorientation; (6) hemiparesis on the side opposite the occlusion of sudden or gradual onset and usually preceded by few or many attacks of fleeting symptoms, as noted above; (7) intracranial systolic bruit on the side opposite the occlusion; (8) reduced or absent pulsation of the internal carotid artery as palpated over the pharyngopalatine muscle in the throat, on the side of the occlusion, and (9) lowered retinal artery pressure on the side of the occlusion.

Fig. 1.—Bulbar conjunctival vessels, photographed one year after thrombosis of the right internal carotid artery, demonstrated by arteriogram. Dilatation of the large and relative paucity of the minute vessels can be seen in the picture of the eye on the side of the occlusion. *A*, right eye; *B*, left eye.



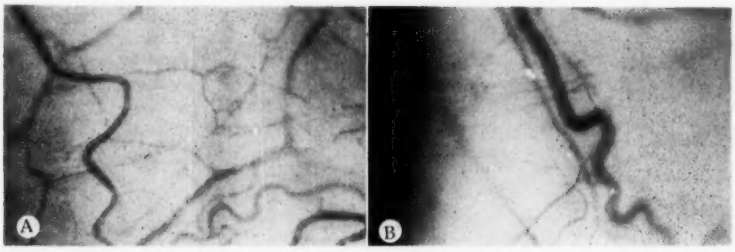


Fig. 2.—Bulbar conjunctival vessels, photographed 10 months after thrombosis of the left internal carotid artery, demonstrated by arteriogram. Dilatation of the large and a paucity of the minute vessels can be seen in the picture of the left eye, on the side of the occlusion. *A*, right eye; *B*, left eye.

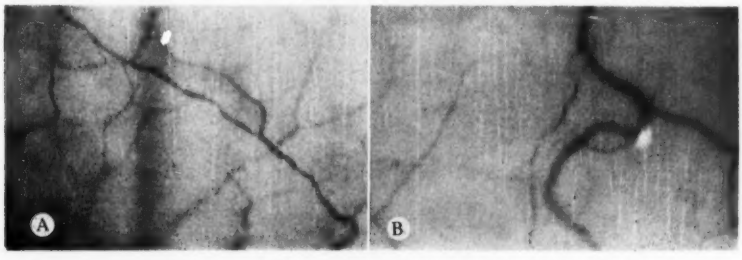
slit lamp, the diameter of the larger bulbar conjunctival vessels was seen to be increased on the side of the occlusion in four of the five patients with proven occlusion of the internal carotid artery due to thrombosis, in four in whom occlusion from thrombosis of the internal carotid artery was extremely likely, and in two patients with occlusion of the common carotid artery: one due to thrombosis, the other to ligation. This dilatation involved specifically arteries, arterioles, veins, and venules and was not evident in the minute vessels of the bulbar conjunctiva. Indeed, the latter were decreased in number and diameter. Dilatation of arteries, arterioles, veins, and venules, with the accompanying paucity of minute vessels, is illustrated in Figures 1, 2, 3, and 4. The large dilated vessels were dark in color. This was specially notable in the right eye of the patient who had had a ligation of the right common carotid artery one and one-half years previously.

Such significant differences in the caliber of the vessels between the two eyes were not observed in the 30 patients with other vascular disease or in the 12 healthy subjects.

One patient among the 30 with other vascular diseases had a protrusion of the left eye due to a cavernous sinus-internal carotid artery fistula (as demonstrated by arteriogram) and presented striking conjunctival edema and dilatation of both large and minute vessels, a picture (Fig. 5) very different from that observed in patients with occlusion of the common or internal carotid artery (Figs. 1-4).

B. Slowed Velocity of Blood Flow in Bulbar Conjunctival Vessels on Side of Occlusion: In minute vessels of about 10μ-20μ in diameter and in venules and arteries of 30μ-50μ in diameter the speed of movement of the red blood corpuscles was observed and compared in the two eyes and was found to be significantly slower on the side of the occluded internal carotid artery. A similar slowed movement on the side of the occlusion was observed in veins of 60μ-120μ in diameter, in which the speed of the

Fig. 3.—Same patient as in Figure 2. The vessels compared are from a zone nearer to the limbus. Note again the dilatation of the large vessels and the extreme paucity of the minute vessels in the photograph of the left eye, the side of the occlusion. *A*, right eye; *B*, left eye.



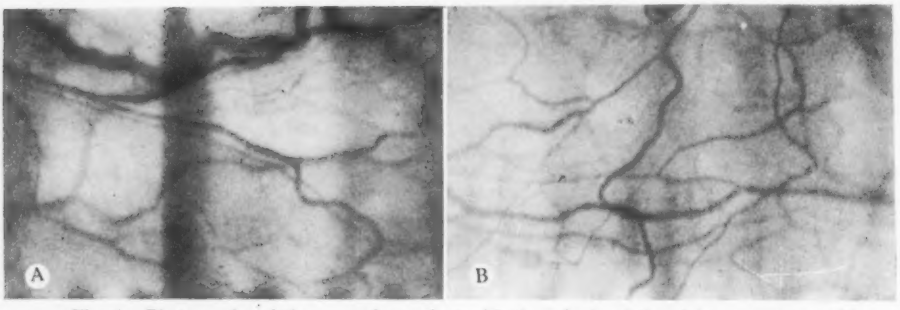


Fig. 4.—Photographs of the eyes of a patient with thrombosis of the right common carotid artery, demonstrated by arteriogram. Dilatation of the large vessels and relative paucity of the minute vessels can be seen in the photograph of the right eye, the side of the occlusion. These photographs were taken eight months after the thrombosis had been demonstrated by arteriogram. *A*, right eye; *B*, left eye.

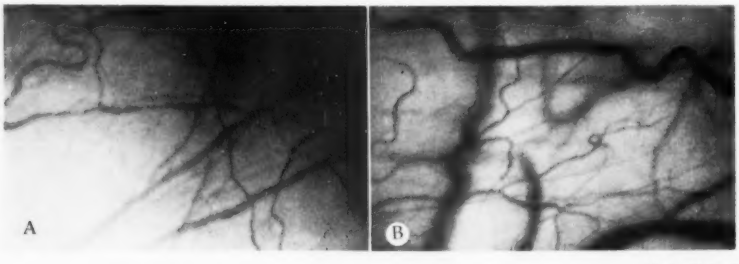
movement of the corpuscles and blood column in the two eyes was readily compared. In arteries of diameter of about 80μ and more, the movement of the blood column could not be detected when its speed was normal. However, on the side of the occlusion, the decreased velocity of the blood flow made visible the movement of the blood column even in these larger arteries, and sometimes it was so slowed that individual red blood cells could be distinguished.

Changes in the caliber of vessels and the speed of flow with occlusion of the common or internal carotid artery were independent of minor fluctuations of the systemic arterial blood pressure. However, the blood pressure in the central retinal artery on the side of the occlusion was low, usually less than half the pressure (in millimeters of mercury) of the other eye.

In one of the five patients in whom thrombosis of the internal carotid artery had been established by arteriography but in whom 25 days previously a right cervical sympathectomy had been performed, the decreased velocity of blood flow and dilatation and ischemia of the bulbar conjunctival vessels were absent. But these findings were present in another patient who was examined three and one-half years after cervical sympathectomy had been performed, homolateral to thrombosis of the internal carotid artery and proven by arteriogram before the operation.

Reversal of the direction of the blood flow in a part of a vessel near a bifurcation, pulsations synchronous or asynchronous with the heart beat, and "sludged blood" occurred no more frequently in patients with occlusion of the common or internal carotid artery than in control subjects. If present, they were seen in both eyes and most frequently in those patients who were markedly arteriosclerotic.

Fig. 5.—Photographs of the eyes of a patient with an arteriovenous fistula on the left (cavernous sinus-internal carotid artery) due to trauma. Dilatation of both large and minute vessels can be seen in the picture of the left eye. *A*, right eye; *B*, left eye.



In addition to the one patient observed 25 days after a cervical sympathectomy, differences in the caliber of the bulbar conjunctival vessels or in the velocity of the blood flow of the two eyes were not seen in the group of 30 patients, as follows: (1) 2 patients who had unilateral thrombosis of the central retinal artery, both of whom had advanced arteriosclerosis and were in cardiac failure and 1 of whom was hypertensive; (2) all patients with thrombosis of the middle cerebral artery or of other intracranial arterial branches than the internal carotid artery, and (3) 1 patient with cerebral hemorrhage due to a congenital arteriovenous abnormality in the deep branches of the middle cerebral artery.

Comment: That ischemia and hypoxia can be the cause of cerebral vasodilatation is well established.[12] Indeed, anoxia of whatever origin causes relaxation of walls of pial vessels in the cat and, if prolonged, can damage them irreversibly.

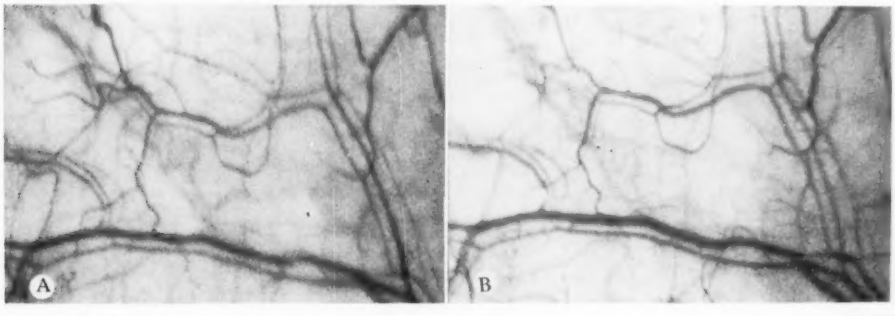
The effects of ischemia due to occlusion of the internal carotid artery have been studied in laboratory animals. Dilatation of the large pial vessels of cats was observed to accompany the clamping of the internal carotid arteries, and the minute vessels were poorly filled.[13] Recently,[14] the effects of ischemia have been studied in the cortex of monkeys during experimentally induced infarction. Dilatation was present in both the arterial and venous branches of the regions examined, and under these circumstances, "venules drain isolated punctate areas in the venous side of the cortical capillary network."

It is likely then that, as in the pial vessels, chronic hypoxia and decreased volume of blood flow, with secondary relaxation of the vascular wall, can explain the dilatation of the larger vessels of the bulbar conjunctiva on the side of the occluded internal or common carotid artery. In contrast, it is inferred that the relative paucity of visible minute vessels results from poor filling of these vessels because of the low blood pressure in the ophthalmic artery. Such an inference is supported by the observed low blood pressure within the central retinal artery.

The fact that the previously described findings in the bulbar conjunctival vessels on the side of occlusion of the internal or common carotid artery were absent in the only one of our patients who had recently had a homolateral cervical sympathectomy but were present in another patient who had had the same operation several months before examination suggests that sympathectomy is followed by an increased blood circulation in the eye but that this effect is not permanent.

It is generally accepted that the retinal and the bulbar conjunctival vascular systems, except for their common origin, are independent of each other. The fact that no impairment of the blood circulation of the conjunctiva was observed in two patients

Fig. 6.—Photographs of the bulbar conjunctival vessels of one eye of an intact subject, a 35-year-old man. Photograph (*A*) was taken before and (*B*) after application of a soap solution to the bulbar conjunctiva after the irritant had been applied. A generalized dilatation of both large and minute vessels can be seen.



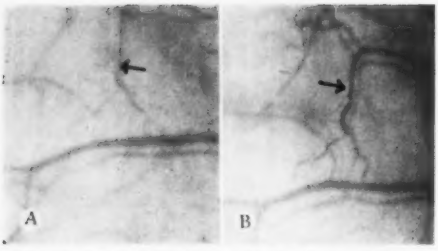


Fig. 7.—Photographs of the bulbar conjunctival vessels of one eye (same intact subject as in Figure 6) before (*A*) and during (*B*) prolonged holding of the breath in inspiration. The dilatation of vessels is most evident in the venules (arrows), presumably from increased intramural pressure within the cranial venous system.

who had unilateral thrombosis of the central retinal artery supports this view.

To define further the mechanism of the effects of occlusion of the internal carotid artery a series of experiments in 12 healthy adults was designed to study in the presence of a sufficient blood supply from the ophthalmic artery the effects of several factors influencing the vascular bed of the bulbar conjunctiva.

Series II

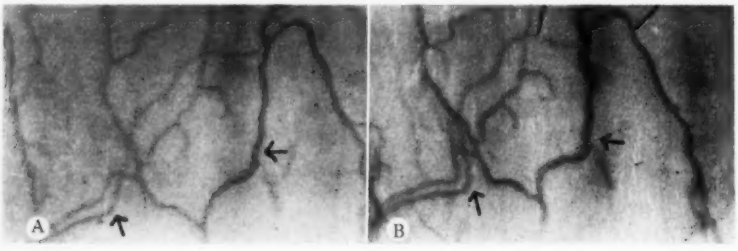
Experimental Observations of Bulbar Conjunctival Vessels in Twelve Intact Subjects.—A. Effects of Mechanical and Chemical Irritation: Vigorous massage of the eye through the lid and chemical irritation of the conjunctiva by means of dilute soap solution produced active dilatation involving arteries and arterioles, veins, venules, and minute vessels (Fig. 6). The blood flow was not decreased in velocity at the height of the vasodilatation and indeed in most instances was significantly increased. The circulating blood became brighter red in color.

B. Effects of Increased Venous Pressure: Prolonged holding of the breath in inspiration produced dilatation of venules, and so minute vessels not usually visible could be seen. Although striking changes were seen in the caliber of the venules, only a slight dilatation of the arterioles was detected (Fig. 7). Similar observations have been made on the pial vessels of cats. Dilatation of arteries and veins was seen after a moderate rise of the venous pressure.[12,15]

C. Effects of Carbon Dioxide Inhalation: A mixture of 95% oxygen and 5% carbon dioxide was administered by face mask to six normal young adults. The inhalation lasted from 60 to 120 seconds. The earliest effect observed on the vessels of the bulbar conjunctiva was bending of arterioles and venules, followed by slight dilatation (Fig. 8). This demonstrates, as already has been shown in the pial arteries of the cat, that the vessels of the bulbar conjunctiva are very sensitive to the action of the carbon dioxide.[13,16] Since bending of the vessels was present before increase in their caliber, it is possible that the carbon dioxide produced relaxation of the longitudinally arranged smooth muscle fibers before it affected the circular fibers.

Hyperventilation did not produce any visible effect on the conjunctival vessels. This may be related to the fact that the

Fig. 8.—Photographs of the bulbar conjunctival vessels of one eye (same intact subject as in Figs. 6 and 7) before (*A*) and after (*B*) the inhalation of a mixture of 95% oxygen and 5% carbon dioxide. Note in the photograph on the right the bending of arterioles and venules at the arrows, which was the first effect of the carbon dioxide. Dilatation can be seen in all vessels. Dark lines at top of *B* indicate (left) artery and, (right) vein.



constrictor effect in the pial vessels of cats after hyperventilation is very much slighter than the dilator effect of the inhaled carbon dioxide.[13]

Summary and Conclusion

The changes in appearance and behavior of the bulbar conjunctival vessels accompanying unilateral occlusion of the common or internal carotid artery were studied in a series of 11 patients by examination of the eyes with a slit lamp.

Thrombosis of an internal carotid artery was accompanied by alterations in the bulbar conjunctiva on the side of the occlusion featured by (*a*) dilatation of arteries and arterioles, veins, and venules; (*b*) a relative paucity of the minute vessels, and (*c*) decreased velocity of the blood flow in all visible vessels. It is inferred that these alterations are due to the effects on the vascular walls of ischemic hypoxia resulting from an insufficient blood supply, an inference supported by the low blood pressure recorded in the central retinal artery of the same eye.

In normal adults (in the presence of a sufficient blood supply from the ophthalmic artery) the vasodilator effects on the bulbar conjunctival vessels of chemical or mechanical irritation, increased venous pressure, and carbon dioxide inhalation have been demonstrated to differ from the effects of ischemic hypoxia. In contrast to the latter, not only arteries and arterioles, veins, and vensules, but also the minute vessels participate in the vasodilatation, and blood flow is not slowed.

The unilateral alterations in the bulbar conjunctival vessels in patients with occlusion of an internal carotid artery were not observed in patients with thrombosis of other intracranial arterial branches or of the central retinal artery.

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Acquired Hemolytic Anemia in Chronic Lymphocytic Leukemia and the Lymphomas

Survival and Response to Therapy in Twenty-Seven Cases

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The presence of severe anemia in patients with chronic lymphocytic leukemia or malignant lymphoma is regarded ordinarily as a bad prognostic sign, often indicating advanced disease or extensive involvement of bone marrow. In some patients, however, marked anemia is due to an overt hemolytic process, and recognition of this fact will lead to proper therapy and a more favorable prognosis.

In 1906, Pappenheim [1] stated that the anemia in lymphocytic leukemia was chiefly myelophthisic in nature but that it was possible in some instances for the anemia to be of hemolytic origin and caused by toxic hemolyzing substances from the tumor tissue. The first report of acquired hemolytic anemia associated with chronic lymphocytic leukemia was given by Paschkis,[2] in 1927. That same year Holler and Paschkis [3] presented the first report of Hodgkin's disease complicated by acquired hemolytic anemia. Since then other cases of Hodgkin's disease, lymphosarcoma, and chronic lymphocytic leukemia associated with acquired hemolytic anemia have been reported.

Submitted for publication Oct. 9, 1958.

Abridgment of thesis submitted by Dr. Kyle to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Fellow in Medicine, Mayo Foundation (Dr. Kyle) and Section of Medicine (Dr. Kiely and Dr. Stickney), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Materials and Methods

Records were studied of patients at the Mayo Clinic from 1945 to 1957, inclusive, who were given the diagnosis of Hodgkin's disease, follicular lymphoma, lymphosarcoma, or chronic lymphocytic leukemia with acquired hemolytic anemia. The underlying disease was chronic lymphocytic leukemia in 16 cases, Hodgkin's disease in 7, follicular lymphoma in 3, and lymphosarcoma in 1. These diagnoses were made by superficial lymph node biopsy in 6 cases, by microscopic examination of the spleen after splenectomy in 3, by peripheral blood smear morphology in 16, and by postmortem examination in 2 others.

Only those cases with unequivocal evidence of overt hemolysis were included in this series. Varying degrees of shortening of survival of red blood cells have been demonstrated in many patients with malignant lymphocytic disease,[4] but in every case of this series the anemia was a significant clinical problem. Criteria for selection included (1) absence of hereditary spherocytosis, (2) presence of significant anemia (hemoglobin less than 9 gm. per 100 ml. of blood), (3) elevated reticulocyte count, (4) elevated indirect bilirubin (above 1.2 mg. per 100 ml. of serum as determined by a modification of Powell's[5] method), (5) elevated fecal excretion of urobilinogen (more than 280 mg. per day as determined by Watson's[6] method), (6) evidence compatible with a hemolytic process in the peripheral blood smear, (7) absence of other causes of hemolysis, and (8) definite histologic diagnosis of all lymphomas and typical evidence of chronic lymphocytic leukemia from peripheral blood smear or bone marrow. Other cases that almost certainly had a hemolytic process were not included because laboratory data were incomplete. All of the cases included in the report met the majority of the criteria listed above. Follow-up information was obtained from local physicians when the patients could not be seen here for further studies.

A differential count of 500 nucleated cells in an unconcentrated bone marrow smear was made in each case from which such material was available. The peripheral blood smear prepared nearest to

TABLE 1.—*Survival After Diagnosis with Physical Findings and Laboratory Data*

Age	Sex	Onset Overt Hemolysis Relative to Diagnosis Underlying Disease, Yr/Mo.		Diagnosis Underlying Disease, Yr/Mo. Until		Size of Spleen *	Adenopathy †	Hemoglobin, Gm/100 Ml.	Reticulocytes, %	Indirect Serum Bilirubin, Mg/100 Ml.	Fecal Urobilinogen, Mg/24 Hr.	Results Coombs' Test	Nucleated Cells in Marrow, %	
		Before	After	Death	Follow-Up								Lymphocytes	Normoblasts
						Hodgkin's Disease								
70	F	0/2		Necropsy		3	1	7.4	1.9	1.6	807	—	9.6	61.2
37	F	Simultaneous			5/9	3	0	5.8	6.6	4.7	307	Positive	25.0	51.4
68	M		0/2	2/8		0	1	4.0	16.0	1.1	357	Negative	30.8	20.0
60	M	Simultaneous		6/3		1	1	2.7	34.0	2.5	1,647	Negative	19.6	42.6
48	F	Simultaneous		9/0		3	1	6.8	21.5	1.58	206	Positive	13.2	57.0
54	F	Simultaneous			4/8	1	2	4.2	33.1	3.4	—	Positive	6.0	67.2
30	M	18/0		Necropsy		1	1	3.9	65.6	2.0	2,091	Negative	12.8	59.2
						Follicular Lymphoma								
66	F	Simultaneous		2/1		3	1	8.3	15.0	2.6	—	—	15.2	47.0
68	F	Simultaneous		2/4		1	2	7.4	6.1	1.8	—	Negative	6.2	47.6
53	M		0/1	1/5		3	2	2.7	16.7	1.4	368	Negative	8.6	63.4
						Lymphosarcoma								
63	M	Simultaneous		0/8		1	1	7.3	24.9	2.0	—	Positive	25.2	45.8
						Chronic Lymphocytic Leukemia								
70	F		3/0		4/0	2	0	8.0	12.2	0.36	—	—	51.2	35.4
64	M		1/1	3/0		1	1	4.2	44.5	4.7	—	Positive	50.0	37.4
69	M		2/6	2/6		1	0	5.8	22.7	2.5	409	—	53.4	29.2
56	M		14/0	16/0		2	2	6.0	8.8	1.7	498	—	75.6	12.4
49	F		2/1		5/4	0	1	8.6	21.9	1.84	384	Positive	55.6	24.6
60	F		3/5	6/1		2	1	4.6	47.9	7.0	—	Positive	40.0	43.0
58	M		3/0	5/0		3	1	3.5	16.4	5.3	1,343	Positive	81.8	12.8
55	M	Simultaneous			1/0	2	1	5.3	40.9	1.99	—	Positive	65.0	20.0
65	F		0/10		2/5	3	1	7.0	8.8	0.8	571	Negative	77.6	10.6
56	F		0/3		3/2	3	1	7.8	18.7	1.0	478	—	—	—
58	F	Simultaneous		0/8		2	1	3.8	32.6	5.04	1,583	Positive	—	—
71	M	Simultaneous		0/1		1	2	3.5	18.7	5.6	618	Negative	96.8	2.2
56	M		4/3	4/3		1	2	6.6	29.0	5.7	—	—	—	—
70	M	Simultaneous		Not traced		2	2	4.1	42.7	3.9	—	—	—	—
80	M	Simultaneous			4/1	1	1	7.8	17.4	1.6	—	Positive	—	—
71	M		2/11	3/5		2	1	6.5	14.2	1.2	233	Negative	23.0	46.6

* 0 indicates not palpable; 1, 2 fingerbreadths below costal margin; 2, from 2 fingerbreadths below costal margin to level of umbilicus, and 3, below level of umbilicus.
† 0 indicates none; 1, moderate, and 2, marked.

the time of the bone marrow aspiration was examined. Coombs' tests were done in the manner recommended by Hare and associates.[7]

Findings and Comparative Reports

Symptoms. — The presenting symptoms could be attributed to the hemolytic anemia in 9 of the 11 patients with lymphoma. In only two was the diagnosis of the underlying disease made before the onset of overt hemolysis, and in each of these the interval between the onset of symptoms and diagnosis was two months or less.

In 11 of the 16 cases of chronic lymphocytic leukemia the initial symptoms were due to the leukemia or the disease was diagnosed by routine blood studies. The diagnosis of chronic lymphocytic leukemia was made an average of 28 months prior to the onset of overt hemolysis. Rosenthal and coworkers [8] found that in 11 cases an average of 33 months elapsed from the time of diagnosis of chronic lymphocytic leukemia until symptoms of hemolysis appeared.

Physical Examination.—Pallor was noted in all patients, and clinical icterus was found in 15. Splenomegaly was found in 25 of the 27 but was of marked degree in only 8 (Table 1). The liver was enlarged in 20 cases. Lymphadenopathy was present in 24 patients but was considered as marked in only 7 (Table 1). A large spleen in the presence of only slight to moderate lymphadenopathy has been observed by others [8] and may contribute in some fashion to the development of hemolytic anemia.

Laboratory Data.—The level of hemoglobin can be seen in Table 1. All patients with chronic lymphocytic leukemia except one had leukocyte counts of more than 50,000 per cubic millimeter of blood at some time during the course of their disease. In 10 of the 16 patients with chronic lymphocytic leukemia the leukocyte count exceeded 150,000.

Some time during the course of the disease the platelet count was less than 100,000 in 18 cases and was less than 50,000 per cubic millimeter of blood in 8 of them. (The normal platelet count in our laboratory varies from 100,000 to 250,000 per cubic millimeter.) All except one of these patients with platelet counts of less than 50,000 had received irradiation, mechlorethamine hydrochloride (nitrogen mustard), or triethylene melamine prior to the onset of thrombocytopenia. No significant hemorrhagic manifestations were seen in any of these patients. Crosby and Rappaport [9] found that the platelet count was less than 100,000 per cubic millimeter in half of their 16 patients with symptomatic hemolytic anemia associated with malignant lymphoma.

The sedimentation rate (Westergren method) was more than 100 mm. per hour in 11 of 19 patients. Some of this elevation might be attributed to the anemia, but more likely it was due to the underlying malignant lymphocytic disease.

Only one patient had a reticulocyte count less than 6% (Table 1). Crosby and Rappaport [9] reported that 10 of their 16 patients with symptomatic hemolytic anemia associated with malignant lymphoma had reticulocytopenia.

The indirect serum bilirubin level was 1.4 mg. per 100 ml. or greater in 22 of the patients during an episode of hemolysis (Table 1). In a reported group of 24 cases,[8] 17 had indirect serum bilirubin findings of 1.0 mg. or more.

Stool specimens adequate for determinations of fecal urobilinogen were obtained from 16 patients. Fourteen of this group excreted more than 300 mg. per 24 hours (Table 1). In another series of 11 patients with malignant lymphocytic disease and hemolytic anemia,[8] 5 patients excreted more than 280 mg. of fecal urobilinogen per 24 hours.

Findings from Coombs' test were positive in 11 of 19 patients (Table 1). Rosenthal and associates [8] reported that results from Coombs' test were positive in all of 20 cases of malignant lymphocytic disease associated with hemolytic anemia. Crowley and Bouroncle [10] declared similar results from Coombs' test in each of four patients with chronic lymphocytic leukemia and

hemolytic anemia, and de Gruchy [11] noted comparable findings in all of a series of 21 cases of acquired hemolytic anemia.

In contrast—and nearer to our own experience—among 14 cases of symptomatic hemolytic anemia secondary to malignant lymphoma or chronic lymphocytic leukemia reported by Wasserman and colleagues,[12] results of the direct Coombs' test were positive in only 50%. In our series we have found the Coombs' test not particularly helpful in determining either the diagnosis or the response to therapy. Some of the following factors have been suggested to account for the differences in the reported incidence of positive findings from Coombs' tests: (1) variation in reactivity of different lots of rabbit serum, (2) exhibition of the prozone phenomenon, (3) insufficient washing of the patient's erythrocytes before mixing with antiglobulin serum, (4) failure completely to absorb the rabbit serum with normal human erythrocytes before use.[13]

Spherocytes were found in all the peripheral smears, but their numbers were scanty in 19 of the 27 cases. Polychromasia was moderate in 20 smears and mild in the other 7. Anisocytosis was present in all cases. Basophilic stippling, chromatin rests, regenerating macrocytes, and target cells were not uncommon. Normoblasts, in small numbers, were found in the peripheral blood smear in 10 instances. Myeloid immaturity was an infrequent finding. Lymphocytes comprised more than 75% of the leukocytes in all but two patients with chronic lymphocytic leukemia. Rosenthal and co-workers [8] found that spherocytosis of greater or less degree in the peripheral blood was present at some time in all patients during the course of the hemolysis associated with malignant lymphocytic disease. Crosby and Rappaport [9] reported spherocytes or abnormal osmotic fragility in 8 of 16 patients with symptomatic hemolytic anemia associated with malignant lymphoma. Wasserman and associates [12] found that 60% of patients with symptomatic hemolytic anemia had spherocytosis, with consequent increase in osmotic and mechanical fragility.

TABLE 2.—*Duration of Illness in Eighteen Patients with Hemolytic Anemia from Diagnosis of Underlying Disease Until Death*

Duration, Yr.	Hodgkin's Disease	Lymphocytic Lymphoma	Chronic Lymphocytic Leukemia
<1	2	1	2
1-2	1	3	1
3-5			4
6-9	2		1
>9			1

Normoblastic hyperplasia of the bone marrow was a prominent observation among our patients with lymphoma (Table 1). In 10 of 11 patients the normoblastic series comprised more than 40% of the nucleated cells. In contrast, 10 of 11 patients with leukemia had 40% or more lymphocytes in the marrow and only 2 had more than 40% normoblasts. In the two groups of patients with symptomatic hemolytic anemia reported by Stats and co-workers [14] and by Wasserman and associates,[12] marrow normoblasts were more than 35% of nucleated cells in three cases of chronic lymphocytic leukemia, more than 55% in two patients with Hodgkin's disease, and more than 70% in two patients with follicular lymphoma or lymphosarcoma.

Duration of Illness (Tables 2 and 3).—The length of time from definitive diagnosis of the malignant lymphocytic disease until death averaged 3.6 years in Hodgkin's disease, 1.6 years in follicular lymphoma and lymphosarcoma, and 4.5 years in chronic lymphocytic leukemia. The length of time from the onset of the overt hemolytic process until death averaged 7.2 years in those with Hodgkin's disease, 1.6 years in fol-

TABLE 3.—*Duration of Illness in Eighteen Cases from Onset of Hemolysis Until Death*

Duration, Yr.	Hodgkin's Disease	Lymphocytic Lymphoma	Chronic Lymphocytic Leukemia
<1	1	1	5
1-2	1	3	4
3-5			
6-9	2		
>9	1		

licular lymphoma or lymphosarcoma, and 1.1 years in chronic lymphocytic leukemia. It is of interest that survival after onset of hemolysis was much longer in Hodgkin's disease than in follicular lymphoma, lymphosarcoma, and chronic lymphocytic leukemia.

Pathology of the Spleen.—In only five of the eight cases that included splenectomy was evidence of the underlying disease visible on microscopic examination of the spleen. It is thus apparent that histologic examination of the spleen is not an infallible test for the underlying malignant lymphocytic disease. Rappaport and Crosby,[15] in a combined necropsy and surgical series of 14 cases of symptomatic hemolytic anemia and malignant lymphoma, found involvement of the spleen with the lymphoma in all but 1. Rosenthal and co-workers [8] reported that 3 of 12 spleens examined afforded no evidence of malignant lymphocytic disease.

Results of Therapy, and Survival

All of these patients received standard treatment for their underlying malignant lymphocytic disease, including such measures as administration of irradiation therapy, mechlorethamine hydrochloride, triethylene melamine, and blood transfusions.

An effort was made to evaluate the effect of adrenocortical steroids and corticotropin (ACTH) on the underlying hemolytic process during 28 hemolytic episodes in 16 patients. The results of this therapy were excellent in 9 instances, fair in 15, and poor in 4.

Excellent results were those in which the concentrations of hemoglobin, reticulocytes, and indirect serum bilirubin remained normal or close to normal for one year or more after the start of adrenal steroid therapy, and no transfusions were required during this period. In seven of the nine, excellent results were achieved by steroid therapy given for three months or less. Fair results were those in which a rise in hemoglobin levels and a decrease in reticulocytes, serum bilirubin, and transfusion requirements persisted for less than one year. In 10 of the 15 instances thus classified, steroid therapy was given for three months or less. In poor results, little or no improvement in clinical or hematologic findings occurred.

One patient who had received little benefit from cortisone responded dramatically to intravenous administration of corticotropin. Another patient who obtained a complete remission by use of corticotropin had received only a temporary remission by use of cortisone. Because of the short duration of therapy with adrenocortical steroids in most cases, very few serious side-effects from the medication were noted.

The therapeutic response to cortisone and corticotropin was not related to the type of underlying malignant lymphocytic disease. Irradiation therapy, mechlorethamine hydrochloride, or blood transfusions were sometimes given simultaneously with the steroid therapy; the effects of these therapeutic agents on the underlying hemolytic process could not be individually evaluated.

Splenectomy, performed on eight patients, brought complete remission to three and partial remission to one; but the remaining four derived no benefit from the procedure. It must be emphasized that the interpretation of these results of splenectomy is difficult because several patients received more than one therapeutic agent at a time and also complete follow-up data on all the patients was not obtainable.

Five patients in this series were neither splenectomized nor given cortisone or corticotropin. Among these, the maximal survival time after onset of overt hemolysis was eight months and the average was two and one-half months.

Dameshek and Komninos [16] reported that 12 of 19 patients having autoimmune hemolytic anemia associated with malignant lymphocytic disease responded excellently to adrenocortical steroid therapy. Five patients had only a fair response, and two received no benefit. Wasserman and co-workers [12] found that cortisone gave a good result in three cases, fair benefit in three, and no help in two. Corticotropin gave good results

in the two cases of their series in which it was used.

Dacie and Chertkow [17] reported that splenectomy gave good results in only two of seven patients with symptomatic hemolytic anemia associated with chronic lymphocytic leukemia or reticulum-cell sarcoma. Hagen and Watson [18] found that splenectomy was highly effective against the hemolytic process in four of six patients with hemolytic anemia associated with chronic lymphocytic leukemia although the remaining two patients received less benefit. Dameshek and Komninos [16] reported that none of their five patients subjected to splenectomy obtained a good result, and Wasserman and associates [12] stated that only one patient of five in their series responded well to splenectomy.

Follow-Up.—At the time of writing, 8 of the 27 patients in our series are living. Six have no particular trouble from either the malignant lymphocytic disease or the hemolytic process, and mild hemolysis continues in two others. Eighteen patients are dead. Eight are known to have died from a combination of hemolysis and the underlying disease; four were not suffering hemolysis at the time of death. No details concerning the death of the other six are available. No follow-up information of any kind could be obtained on one patient.

Summary and Conclusion

Laboratory data, results of therapy, and survival after diagnosis in a group of 27 cases of overt hemolytic anemia secondary to chronic lymphocytic leukemia or malignant lymphoma are reported. The hemolytic anemia was responsible for the initial symptoms and led to the diagnosis of the underlying disease in the majority of patients with lymphoma, whereas in most of the patients who had leukemia the hemolytic anemia was a later development. Survival time after the onset of the overt hemolytic process averaged 7.2 years in those with Hodgkin's disease, 1.6 years in those with follicular lymphoma and lymphosarcoma, and 1.1 years in those with chronic lymphocytic leukemia.

Splenectomy benefited only four of eight patients.

Corticotropin (ACTH) or adrenocortical steroids were of definite benefit in controlling the hemolytic state in the majority of patients so treated. The recognition of complicating overt hemolytic anemia during the course of chronic lymphocytic leukemia or malignant lymphoma is important if proper therapy is to be given, for, although adrenocortical steroids and corticotropin have little to offer the usual patient with chronic lymphocytic leukemia or malignant lymphoma, in a patient with complicating symptomatic hemolytic anemia these drugs often produce remarkable improvement.

Mayo Clinic.

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Effect of Carbonic Anhydrase Inhibitors on the Course of Sickle-Cell Disease

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The inhibition of carbonic anhydrase in the mature erythrocyte has been utilized by Hilkovitz [1] as a therapeutic measure in the treatment of sickle-cell disease. Evidence presented in his observations suggests that definite beneficial results may be expected when the inhibitor, acetazolamide, is administered in the recommended dosage. The logic of this procedure, as presented, is based on the knowledge that carbonic anhydrase, an enzyme present in the mature erythrocyte, catalyzes the reversible reaction $H_2CO_3 \rightleftharpoons CO_2 + H_2O$. Inhibition of this reaction in sickle-cell disease could presumably affect the degree of hemoglobin reduction and diminish in vivo sickling, with a subsequent increase in erythrocyte count. His optimistic approach to the therapy of sickle-cell disease warranted further evaluation. The purpose of this communication is to present our findings after administration of comparable amounts of carbonic anhydrase inhibitors to subjects having sickle-cell disease.

Clinical Material

Four adult patients having sickle-cell disease were studied. Electrophoretic patterns, genetic histories, and searching blood studies confirmed homozygous S disease. Previous periods of clinical observation of these patients extended from 1 year (Case 4) to 10 years (Case 3). Cases 1 and 2 were observed for approximately five years. Three of the subjects were females, and one, Case 3, was a male. Cases 2 and 3 had frequent and relatively severe crises. Case 3 was under observation in the hospital on two occasions; the first period was for 49 days, and the second period extended from the fifth to the seventh month of study. Hospitalization was necessary because of severe and recurrent crises associated with clinical and x-ray evidence of pulmonary consolidation. She also had ulcers of both lower extremities, which were refractory to treatment. The other three subjects were ambulatory.

Submitted for publication Sept. 2, 1958.

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The investigations of the authors are supported by the J. Ernest Wilkins Research Fund of the Kappa Alpha Psi fraternity and by the D. T. Burton Research Foundation.

Plan of Study

Two carbonic anhydrase inhibitors were utilized: acetazolamide (Diamox, Lederle) and ethoxzolamide (Cardrase, Upjohn), the latter supposedly a more potent inhibitor. The following observations were made: (1) the immediate effect of a carbonic anhydrase inhibitor after oral administration of a single dose and (2) the effect of long-term daily administration of the medication. This period of observation extended from one month in Case 2 to seven months in Case 3. At the first hospital admission, Case 3 was immediately started on asetazolamide. At the fifth month (second admission to the hospital) acetazolamide was discontinued and ethoxzolamide was given. Case 2 was given acetazolamide, while the others were given ethoxzolamide. Indicated laboratory studies included (1) determinations of the degree of in vivo sickling, (2) erythrocyte and hemoglobin determinations, and (3) variations in sedimentation rates of erythrocytes containing oxygenated and reduced hemoglobins (diagnostic parameter). Leukocyte counts, differentials, and serum bilirubins were also obtained. Our criteria of benefit in the therapy of sickle-cell disease are (1) an increase in erythrocyte count, (2) diminution in the degree of in vivo sickling, and (3) improvement in the clinical symptoms.

Results

In Table 1, the results of acute administration of the carbonic anhydrase inhibitors are presented. Variations in in vivo sickling are noted, but these are inconstant and apparently nonspecific. Increase in diag-

TABLE 1.—*Effect of Acute Administration of Carbonic Anhydrase Inhibitors in Sickle-Cell Disease*

Case	Carbonic Anhydrase Inhibitor	Dose, Mg/Kg.	Before				After				
							2d Hr.	3d Hr.			
			In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter	In Vivo Sickling, %	In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter
1	Ethoxzolamide	8	20	2.44	8.7	33	16	16	2.44	8.3	39
2	(1) Acetazolamide	7.2	37	2.3	10	16	40	43			15
	(2) Acetazolamide	7.2	55	2.59	9	39	54	43	3.01	8	46
3	(1) Acetazolamide	10	31.7	2.10	7	33	40	53	2.80	7	50
	(2) Acetazolamide	10	50				46	53			

nostic parameter, after a single oral dose, is to be further evaluated. Effects of prolonged administration of the carbonic anhydrase inhibitors are noted in Table 2. No specific benefit of therapy is seen. Only studies of importance to this communication are presented in both tables.

Temporary weight loss and slight increase in the erythrocyte count occurred in Case 3. Thorough evaluation of the effect of the inhibitors on these phenomena was prevented because of the severe crisis at the beginning of therapy. Two episodes of pain and one period of disorientation were noted during treatment. Consistent lowering of the CO_2-combining power and increase in serum chlorides occurred. Serum bilirubin determinations, leukocyte counts, and differential blood smears revealed no unusual change in any of the subjects.

Comment

Pauling and associates [2] definitely demonstrated that the basic defect for the sickling phenomenon was a mutant form of hemoglobin. With use of the technique of electrophoresis, they demonstrated a difference in mobility between hemoglobin from normal subjects and those having sickle-cell disease. These differences in mobility were dependent upon variations in electrical charges. Recently, Ingram,[3] by exhaustive studies of the hemoglobin molecule in normal subjects and those having sickle-cell disease, found that the positioning of an amino acid, in what he labels the No. 4 peptide group, may explain the variation in electrical charge. Later, hemoglobin C variation could be explained in a similar manner. Exactly why hemoglobin S diseases are associated with bizarre changes in the erythrocyte under reduced oxygen tension or why irreversibly sickled cells occur has not been adequately explained. Other hemoglobin mutants, although responsible for mild symptoms, still maintain their shape even when oxygen tension is reduced. The bizarre forms, associated blood viscosity, and slowing of the blood flow are believed to be responsible for the occlusive phenomena occurring in the small blood vessels that result in the clinical crisis.[4]

Symptoms of sickle-cell disease are frequently severe and debilitating, although cases have been reported whose clinical manifestations were only weakness and easy fatigability that may persist for years.[5] The usual benign adult clinical picture is that of an eunuchoid habitus, persistent anemia, evidence of increased continuous erythrocyte destruction, and bone marrow hyperactivity. Adequate compensatory mechanisms may allow the subject to withstand even marked lowering of oxygen tension without clinical effect.[6] The crisis can be called an unpredictable, pernicious, sometimes frequent complication that occurs during the course of a disease to which a patient has become otherwise adjusted.

It has been our experience that painful episodes can result when blood flow is slowed. This is observed when massive doses of adrenal steroids are administered

TABLE 2.—*Effect of Prolonged Administration of Carbonic Anhydrase Inhibitors in Sickle-Cell Disease*

Case	Carbonic Anhydrase Inhibitor	Dose, Mg./Kg.	Before				After															
							1 Mo.				2 Mo.				5 Mo.				7 Mo.			
			In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter	In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter	In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter	In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter	In Vivo Sickling, %	RBC, Millions	Hgb., Gm.	Diagnostic Parameter
3	Acetazolamide	9.5	54	1.59	6 (crisis)	57	31.7	2.10	7	33					53	1.80 (crisis)	7	66	61	1.47	6.5	48
																	Cardrase, 4.5 mg./kg.					
4	Ethoxzolamide	5.5	33	3.2	8.5	29	23	2.27	7.25	29	28	2.81	7.5	26								
1	Ethoxzolamide	4	20	2.44	8.7	33					26	2.06	6.9	32								
2	Acetazolamide	7.2	37	2.3	8	16	55	2.59	9	38												

or occasionally when adrenalin is given in significant amounts. Variations in the sedimentation rate between oxygenated and reduced erythrocytes, as noted in vitro, may also play a significant role in the production of symptoms. Studies have shown that no definite correlation can be made between the onset of painful episodes and the degree of in vivo sickling in patients having sickle-cell disease.[7] Marked variations in the sedimentation rates, with formation of large clumps in the oxygenated state, are usually observed in patients having severe crises. Microscopic examination of these clumps will also reveal some irreversibly sickled cells; although the others are in the normal shape of the erythrocyte. Blood sludging, irreversibly sickled cells, and slowing of blood flow to an organ may be incriminated as the causative factor of a crisis. Combinations of these phenomena could explain the occasional findings of splenic infarction noted at high-altitude flying,[8] hematuria,[9] lowered renal concentration,[10] and unexplained deaths [11] that may occur in persons having only the sickle-cell trait.

Utilization of a carbonic anhydrase inhibitor to prevent these pathophysiological changes of sickle-cell disease is of interest. From our observations, however, as well as those of others [12] interested in the therapy of this disease, the use of these inhibitors is of no practical benefit. The recent report of Greenberg and Kass [13] would indicate that any resulting acidosis that might occur could result in increased sickling. Based on the studies of Neel,[14] Pauling,[2] and Ingram,[3] it would appear that this hereditary disease can be eliminated only by corrective measures which would prevent the basic defect.

Conclusions

Carbonic anhydrase inhibitors were administered to four adult patients having sickle-cell disease. Periods of observation extended from two hours to seven months. No effect of importance could be noted. Variations in in vivo sickling, erythrocyte

count, and sedimentation rate between cells containing oxygenated and reduced hemoglobins were not significant enough to be indicative of value.

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Iproniazid Hepatitis

Report of Five Cases and Review of Pertinent Literature

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Iproniazid * (1-isonicotinyl-2-isopropyl-hydrazine) was initially introduced to clinical medicine as an antituberculous agent in 1952.[1] Although potent in its therapeutic effect, the drug was eventually abandoned in favor of its chemical relative, isoniazid, largely because of its distressing side-effects. In addition to its antituberculous activity, early studies with iproniazid clearly indicated a striking nonspecific action in promoting elevation of mood, stimulating appetite, and increasing sense of well-being. In view of these nonspecific effects, the drug has been recently reintroduced as a "psychic energizer" in the management of psychiatric depression, with favorable results.[2,3] Furthermore, there are indications that this agent is now being used in a large variety of medical disorders. Reports concerning the use of iproniazid in hypertension,[4] rheumatoid arthritis,[5] and angina pectoris [6] have already appeared in the literature.

Of the early-recognized side-effects of iproniazid, those resulting from undesirable actions on the autonomic and central nervous systems are most frequent. These include vertigo, insomnia, hyper-reflexia, muscular twitching, convulsions, paresthesias, postural hypotension, dry mouth, delayed micturition, and constipation. Perhaps the most serious, and certainly the least-documented toxic effect, is jaundice. In an effort to clarify further the status of jaundice as a significant toxic effect of iproniazid therapy, the following five case reports and review of pertinent literature are presented.

Submitted for publication Oct. 27, 1958.

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* Available as Marsilid from Hoffmann-La Roche, Inc., Nutley, N. J.

Report of Cases

CASE 1.—A 49-year-old white woman was admitted to Montefiore Hospital on Jan. 25, 1958, because of jaundice of two weeks' duration. Iproniazid therapy had been instituted two months prior to admission because of depression. After a four-week period of treatment, during which time she took 150 mg. of iproniazid daily for a total of 4.2 mg., the drug was discontinued. Two weeks after cessation of therapy, the patient first noticed jaundice, dark urine, and light-colored stools. Liver-function tests three days prior to admission revealed a total serum bilirubin of 8.2 mg. %, cephalin flocculation of 3+, thymol turbidity of 10.0 units, and alkaline phosphatase of 5.5 Bessy-Lowry units. The patient denied all gastrointestinal symptomatology. Although an oral cholecystogram performed three years previously revealed a single gallbladder calculus, she specifically denied previous jaundice as well as recent fever, abdominal pain, dyspepsia, or vomiting. She did not drink alcoholic beverages and was not exposed to jaundiced persons, injections, or hepatotoxic agents, excluding iproniazid, for at least six months. Her only other medication during this period was an occasional capsule of secobarbital at bedtime.

Physical examination revealed a well-nourished, grossly icteric but alert, middle-aged woman in no acute distress. The temperature was 99 F; the pulse rate, 72, and the blood pressure, 160/90. There were no significant physical findings except jaundice and a soft, nontender liver edge palpable 6 cm. below the right costal margin in the midclavicular line.

Liver-function tests on admission revealed a total serum bilirubin of 18.0 mg. %, cephalin flocculation of 3+, thymol turbidity of 10.0 units, and alkaline

TABLE 1.—*Liver-Function Studies in Our Four Patients Developing Jaundice After Iproniazid Therapy*

	Date, 1958	Bilirubin				Cholesterol					
		Total, Mg. %	1 Hr. Mg. %	Alb., Gm. %	Glob., Gm. %	Total, Mg. %	Esters, Mg. %	Alk. P'Tase, Units *	Ceph. Flocc.	Thymol Turb., Units	SGOT, Units
Case 1	1/22	8.2		3.3	3.8			6.5	3+	10.0	
	1/25	18.0		3.5	3.2			4.7	4+	15.0	
	1/30	18.6						5.3	4+	14.0	945
	2/3	21.4		2.5	4.4	195			4+	13.0	444
	2/7	14.1		3.6	3.1			3.6	4+	14.0	225
	2/12	7.4		3.3	3.6			3.7	4+	18.0	153
	2/20	3.1		3.5	3.1			3.6	4+	5.0	132
	2/28	2.5		3.7	3.2			2.5	4+	4.0	69
	3/10	1.7		4.0	3.5	264		2.4	2+	6.0	36
Case 2	2/24	10.2						14.6	4+	12.2	
	3/1	16.2						8.8	4+	26.0	2,200
	3/6	38.0		3.9	4.9	161		6.9	4+	23.0	2,000
	3/8	45.6		4.2	4.4	145		8.5	4+	20.0	700
	3/14	44.5		3.3	3.5	108		7.6	4+	14.0	495
	3/16	57.2						7.4	4+	11.0	308
Case 3	5/21	7.8						28.8	4+	5.7	
	5/28	22.4	14.0	2.8	3.8	170		36.3	4+	9.6	
	6/6	19.2	11.0	2.5	3.9	209		37.6	4+	11.8	
	6/11	16.8	11.0	2.5	4.5	222		37.7	4+	11.8	860
	6/16	13.8	7.4	2.3	4.2	226	58	48.0	3+	12.2	
	6/24	7.4	2.8	2.3	4.3	255	128	33.1	2+	10.9	
	7/2	3.8	1.8	2.9	3.9	264		42.5	0	4.4	
	7/14	1.5	0.7	2.7	3.4	264	211	21.6	0	5.9	
	7/25	1.3		3.4	3.8	304	235	18.0	0	3.3	
	8/12	0.7		3.3	3.0	265	206	11.8	0	2.8	
	8/22	Sulfobromophthalein retention- 3%									
Case 4	9/18	9.5		4.3	2.8	209		11.5	4+	8.0	1,300
	9/28	16.4						5.6			1,325

* Cases 1, 2, and 4, Bessy-Lowry units, normal range 0.8-3.0; case 3, Shinowara units, normal range 2.2-8.6

phosphatase of 6.5 Bessy-Lowry units. These and subsequent liver-function tests are tabulated in Table 1. All other laboratory data were largely within normal limits. The hematocrit varied between 40% and 44%, and the leukocyte count, between 4,400 and 9,300 per cubic millimeter. Eosinophilia, ranging from 6% to 12%, was noted consistently in all peripheral blood smears. A scout film of the abdomen demonstrated a single, 4 mm. calculus in the area of the gallbladder.

The patient was afebrile and asymptomatic throughout her hospital stay despite increasing jaundice during the first hospital week. Treatment consisted of bed rest, high-carbohydrate low-fat diet, and vitamin supplements. Laboratory improvement was first noted on the 10th hospital day, and icterus gradually declined during the subsequent five weeks. The decline in serum bilirubin was closely paralleled by a progressive fall in serum glutamic oxalacetic transaminase levels from a maximum of 945 to 36 units at the time of discharge. The patient was released from the hospital on March 10, 1958, eight weeks after the onset of jaundice, at which time her total serum bilirubin was 1.7 mg. %. The patient subsequently continued to do well, and at present no sequelae are evident.

Comment.—Despite the presence of cholelithiasis in this patient, her episode of jaundice is clearly attributable to hepatocellular damage, as evidenced by the liver-function tests. In the absence of cirrhosis, exposure to other hepatotoxic agents, or positive evidence to suggest viral hepatitis, including the absence of fever, the diagnosis of toxic hepatitis due to iproniazid therapy was considered most likely. The persistent eosinophilia noted in this patient could not be explained. The possibility that this finding was a reflection of iproniazid hypersensitivity was considered.

CASE 2.—A 68-year-old white woman was admitted to Montefiore Hospital on March 1, 1958, because of jaundice of two weeks' duration. During the two months prior to admission, the patient took 50 mg. of iproniazid daily (total dose 3.0 gm.) for

mild depression. There was a past history of recurrent episodes of acute cholecystitis with jaundice for many years, with several roentgenologic studies of the gallbladder revealing nonvisualization. On Dec. 6, 1957, at which time the patient was anicteric, a cephalin flocculation of 4+ and total serum cholesterol of 300 mg. % were noted. Liver-function tests on Feb. 24, 1958, one week after the onset of her recent episode of jaundice, revealed a total serum bilirubin of 10.2 mg. %, cephalin flocculation of 4+, thymol turbidity of 12.2 units, and alkaline phosphatase of 14.6 Bessy-Lowry units. The patient complained only of mild anorexia. Her current jaundice was unassociated with abdominal pain or vomiting. There was no history of alcoholism or contact with jaundiced persons or hepatotoxins, excluding iproniazid; recent injections, or blood transfusions.

Physical examination revealed a fairly well-nourished, alert, well-oriented, icteric white woman. The temperature was 99 F; the pulse, 80, and the blood pressure, 150/70. Jaundice and a liver edge palpable 4 cm. below the right costal margin in the midclavicular line were the only significant physical findings.

Liver-function tests on admission revealed a total serum bilirubin of 16.2 mg. %, alkaline phosphatase of 8.8 Bessy-Lowry units, cephalin flocculation of 4+, thymol turbidity of 26.0 units, and a serum glutamic oxalacetic transaminase level of 2,200 units. All live-function tests performed during the patient's illness are tabulated in Table 1. All other laboratory studies on admission were not remarkable, except for mild hyperglycemia. The hematocrit was 34% and the leukocyte count 5,800 per cubic millimeter. No eosinophilia was noted in the peripheral blood smear.

The patient was initially treated solely with bed rest, but on March 7, 1958, the patient was started on 40 mg. of prednisone daily because of the excessively high serum transaminase level (2,000 units). The patient remained alert and asymptomatic, however, until March 8, 1958, at which time she was noted to be lethargic, tremulous, and slightly disoriented. Her total serum bilirubin at this point had increased to 45.6 mg. %. Prednisone was increased to 60 mg. daily, and a low-protein diet, intravenous hydration, and oral chloramphenicol therapy instituted. Her subsequent course was characterized by the rapid development of hepatic coma terminating in death on March 12, 1958, despite intensification of steroid therapy and the administration of glutamate salts. It is noteworthy that a progressive fall in serum glutamic oxalacetic transaminase level from 2,200 units to 308 units continued throughout her course, despite rapid clinical deterioration during the final three days of life. It should also be noted that the patient remained afebrile throughout her illness.

Autopsy revealed two distinct hepatic abnormalities. Associated with chronic cholecystitis and cholelithiasis, chronic intrahepatic pericholangitis and fibrosis (biliary cirrhosis) were noted. The more striking lesion, however, was widespread focal necrosis of liver parenchyma (Fig. 1).

Comment.—The terminal episode of jaundice in this patient could not be attributed to her biliary cirrhosis. The liver-function tests during life and widespread necrosis of liver cells found at autopsy are ample evidence that diffuse hepatitis was primarily responsible for her final illness and death. The untoward contribution of her previously existing liver disease to the fatal termination cannot, of course, be denied. In the absence of positive evidence

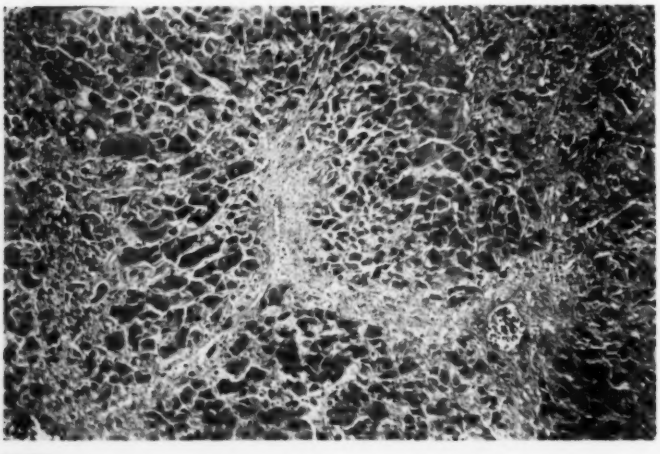

Fig. 1 (Case 2).—Section of liver obtained at autopsy. Area of coagulation necrosis infiltrated by mononuclear inflammatory cells. Hematoxylin and eosin; reduced about 35% from mag. × 140.

to suggest any other etiology, her diffuse hepatitis was attributed to iproniazid therapy.

CASE 3.—A 64-year-old white man was admitted to the psychiatric service of the Bronx Veterans Administration Hospital on Nov. 1, 1957, because of agitated depression following a suprapubic prostatectomy performed in June, 1957, for benign prostatic hypertrophy. At the time of prostatectomy, the patient received a single transfusion of 500 cc. of whole blood. In July, 1957, the patient underwent meatotomy for urethral stricture and while hospitalized received 100 mg. of chlorpromazine daily for a period of two weeks because of agitation. The patient's complaints on admission were related solely to depression. Aside from disinterest in food, the patient denied all gastrointestinal symptomatology. The patient admitted to only occasional social indulgence in alcoholic beverages and denied exposure to any jaundiced persons or potentially hepatotoxic agents, aside from the single blood transfusion and course of chlorpromazine therapy noted above.

Physical examination, performed on the psychiatric service, was noted to be essentially negative. Psychiatric evaluation revealed gross evidence of agitated depression.

Initial laboratory studies were not remarkable except for albuminuria and pyuria consistent with chronic cystitis. Liver-function studies were not done on admission.

The patient was initially treated with 100-150 mg. of chlorpromazine daily for three weeks. The response to chlorpromazine was minimal, and the drug was discontinued on Nov. 28, 1957. During the month of December, 1957, he received 14 electroshock treatments, with equivocal benefit. The patient was also treated for chronic cystitis almost throughout his hospital course, initially with sulfamethoxypyridazine (Kynex) which was discontinued Dec. 31, 1957, and subsequently with tetracycline. On March 22, 1958, the patient developed acute left epididymitis, which responded readily to conservative measures and penicillin.

On April 8, 1958, therapy with iproniazid was instituted. The patient received 200 mg. daily from April 8 to 15, 1958, and 100 mg. daily from April 16 to May 20, 1958. Along with iproniazid, the patient was given 100 mg. of pyridoxine daily. Iproniazid was discontinued on May 21 because of a syncopal episode associated with postural hypotension. To that point the patient had received a total dose of 4.9 gm. over a six-week period, with no discernible therapeutic effect. On May 22, the day following cessation of iproniazid therapy, the patient was noted to be grossly icteric. Except for some increased anorexia, he remained symptomatically unchanged. Examination revealed a temperature of 98.6 F, a pulse rate of 88, and a blood pressure of 120/70. A liver edge was now palpable 7 cm. below the right costal margin in the midclavicular line, but the abdomen was otherwise negative. Liver-function tests on May 22 revealed a total serum bilirubin of 7.8 mg. %, alkaline phosphatase of 28.8 Shinowara units, cephalin flocculation of 4+, and thymol turbidity of 5.7 units. These and all other subsequent liver-function studies are tabulated in Table 1. All other laboratory studies during the period of hepatic dysfunction were not remarkable, except for elevation of the erythrocyte sedimentation rate to a maximum of 32 mm. in one hour (Wintrobe method) at the height of jaundice. Hemoglobin levels varied between 11.0 and 14.0 gm. per 100 ml., and leukocyte counts, between 7,000 and 13,000 cubic millimeter. No eosinophilia was noted in repeated peripheral blood smears.

The patient's course was initially one of increasing jaundice and laboratory evidence of severe and progressive liver-cell damage. In spite of this, the patient remained afebrile and appeared surprisingly well clinically. Anorexia, mild ab-

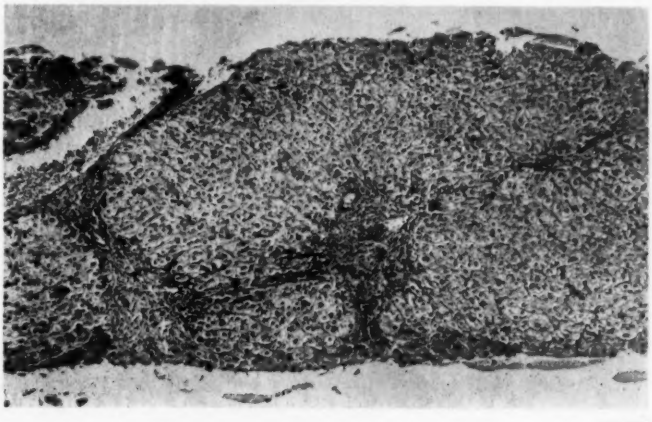

Fig. 2 (Case 3).—Section of needle biopsy of the liver obtained on the 36th day of jaundice. Evidence of healing is most prominent. Distortion of the hepatic architecture by perilobular fibrosis and fibrous septa extending into the lobules is noted. Hematoxylin and eosin; reduced about 35% from mag. × 80.

dominal distention, and generalized pruritus were his only complaints. Treatment consisted of bed rest, high-carbohydrate diet, and vitamin supplements. After a two-week period of increasing jaundice, improvement began, and over the subsequent 10 weeks the patient's serum bilirubin gradually declined to normal levels. At the time of this report, only a mild elevation of the alkaline phosphatase remains as residual evidence of the patient's previous severe liver damage. A sulfobromophthalein determination on Aug. 22, 1958, 14 weeks after the onset of jaundice, revealed only 3% retention.

Liver biopsy (Fig. 2) performed on June 27, 1958, at which time marked laboratory improvement had already occurred, was interpreted by Dr. Hans Popper † as follows:

Chronic hepatitis with beginning perilobar fibrosis, suggesting a tendency for cirrhosis formation, and significant portal inflammation and regeneration. The following features are found, as in conditions usually designated as viral hepatitis: (1) heavy lipofuscin deposition, (2) formation of irregular small septa, and (3) active ductular proliferation surrounded by segmented leukocytes which are not found in the parenchyma.

Comment.—It was our final impression that the patient's episode of severe liver damage represented a toxic effect of iproniazid therapy. There was no evidence of biliary tract disease or previous cirrhosis. The patient had received no blood transfusions for 11 months prior to the onset of jaundice and had not been exposed to hepatotoxic agents, excluding iproniazid, for at least five months prior to the onset of jaundice. Needle transfer of viral hepatitis was considered unlikely in view of the hospital's rigid prophylactic techniques. Although infectious hepatitis could not be ruled out with certainty, the lack of contact with any cases of hepatitis in the hospitatl environment and the absence of fever or prodromal symptomatology militated against this.

Although the liver biopsy suggested early cirrhotic changes, no definite residual impairment of hepatic function could be detected. The patient will be evaluated again in the future for the possibility of postnecrotic cirrhosis.

† Director of Department of Pathology, The Mount Sinai Hospital, and Consultant in Pathology, Veterans Administration Hospital.

CASE 4.—A 48-year-old white man was admitted to Montefiore Hospital on Sept. 17, 1958, because of jaundice and dark urine of one week's duration. During the two months prior to admission, the patient had taken 150 mg. of iproniazid daily (total dose, 9.0 gm.) for depression. There was no previous history of hepatic, biliary, or gastrointestinal disease. The patient complained only of mild abdominal cramps during the three days prior to admission. There was no history of transfusion, injections, or exposure to jaundiced persons or hepatotoxic agents, excluding iproniazid. Liver-function tests, performed as a routine measure on Aug. 28, 1958 (prior to jaundice), revealed a total serum bilirubin of 0.8 mg. %, a negative cephalin flocculation, thymol turbidity of 0.5 units, and a total serum cholesterol of 320 mg. %.

Physical examination revealed a well-nourished, alert, middle-aged white man who was grossly icteric but in no acute distress. The temperature was 99.2 F; the pulse rate, 72, and the blood pressure, 120/80. The only significant findings were scleral icterus and a soft, slightly tender liver edge palpable 4 cm. below the right costal margin in the midclavicular line.

Liver-function studies on admission revealed a total serum bilirubin of 9.5 mg. %, total serum cholesterol of 209 mg. %, cephalin flocculation of 4+, thymol turbidity of 8.0 units, alkaline phosphatase of 11.5 Bessy-Lowry units, and a serum glutamic oxalacetic transaminase level of 1,300 units. The hematocrit was 42%, and the leukocyte count 4,700 per cubic millimeter. A peripheral blood smear revealed a mild relative lymphocytosis but no eosinophilia. A serum protein electrophoresis revealed only a slight elevation of the γ-globulin fraction.

The patient remained afebrile and asymptomatic throughout his hospital stay. The patient left the hospital after a two-week period, although his jaundice was increasing at the time of discharge. He has subsequently been followed carefully at home, and a therapeutic regimen of bed rest and high-carbohydrate low-fat diet, continued. At the time of this report, two weeks after the patient's discharge, he remains afebrile and asymptomatic, although still icteric.

Comment.—There is no positive evidence in this case to suggest any etiology for this patient's evident diffuse liver damage other than iproniazid therapy.

CASE 5.—A 69 year-old white woman was admitted to Montefiore Hospital on Nov. 22, 1957, because of progressive gangrene of the right foot of three weeks' duration. There was a history of arteriosclerotic peripheral vascular disease in the past. A left midleg amputation had been performed in 1955 because of gangrene of the left foot. The patient was a mild diabetic, controlled with dietary

measures alone. She complained only of pain in her foot and moderately severe anorexia. There was no history of hepatic or gastrointestinal disease. The patient denied excessive alcohol intake and exposure to jaundiced persons or known hepatotoxins. She had received no injections or blood transfusions for at least one year prior to admission.

Laboratory data on admission included a hematocrit of 35%, leukocyte count of 8,400 per cubic millimeter, and a normal differential count. Examination of the urine was within normal limits. The fasting blood sugar was 120 mg. %, and the blood urea nitrogen, 18.6 mg. %. Liver-function studies were not done. Culture of purulent material from the right foot revealed coliform bacilli and hemolytic Staphylococcus pyogenes var. aureus.

Physical examination revealed a thin, elderly, white woman, complaining of pain in her right foot. The temperature was 99.2 F; the pulse, 70, and the blood pressure, 170/60. The patient was not icteric, and the liver was not enlarged. The only significant physical findings were absence of palpable peripheral pulses in the lower extremities and infected gangrene of the toes of the right foot.

The patient was initially febrile to 102 F. After two weeks of therapy with penicillin, streptomycin, nitrofurantoin, and local measures her gangrene did not progress and she became afebrile. Her diabetes was largely controlled with diet alone, although occasional injections of 10-15 units of regular insulin were required for excessive glycosuria. On Dec. 11, 1957, iproniazid therapy was instituted in an attempt to stimulate the patient's appetite. The initial dose of 100 mg. daily was increased on Dec. 19 to 150 mg. per day. On Dec. 24, iproniazid therapy was discontinued because of an episode of confusion and involuntary twitching of the lower extremities. The total dose of iproniazid administered during her two-week course of therapy was 1.7 gm. On Dec. 25, the day following cessation of iproniazid therapy, a supramaleolar amputation of the right foot was performed. The patient did poorly postoperatively. Her temperature rose to 101.5 F; her blood pressure fell to 90/60, and she became anuric. The patient died 12 hours after surgery, on Dec. 26, 1957. No pressor agents were given prior to death.

Autopsy revealed severe coronary atherosclerosis, marked generalized arteriosclerosis, and bilateral bronchopneumonia. A striking, unexpected finding was widespread, acute focal hepatitis. Foci of hepatic-cell necrosis surrounded by acute inflammatory reaction and hemorrhage were noted throughout the liver (Fig. 3).

Comment.—This patient was not noted to be icteric at any time. Hepatic disease was not suspected during life, and liver-function studies were not done. The widespread focal hepatic necrosis revealed at autopsy was much severer than that sometimes seen in patients dying in shock. Although the appearance of the hepatic lesions was consistent with viral hepatitis, there was no positive evidence for this diagnosis. The possibility that iproniazid contributed to the production of these lesions was strongly considered. Although death in this case can hardly be attributed to iproniazid alone, the focal hepatic necrosis observed at autopsy undoubtedly contributed to this patient's death.

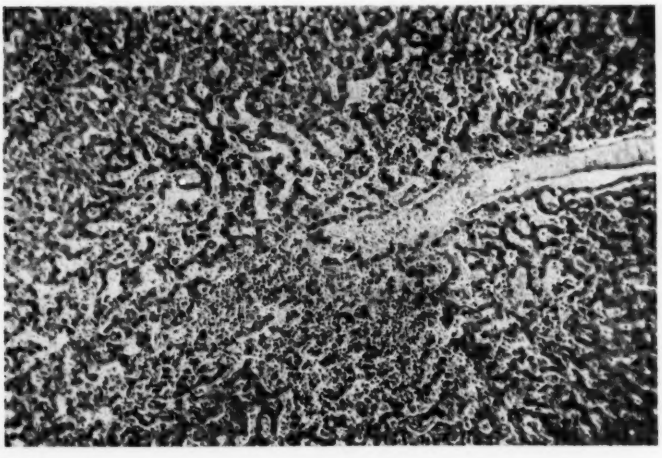

Fig. 3 (Case 5).—Section of liver obtained at autopsy. Focal area of liver-cell necrosis surrounded by acute inflammatory cells and hemorrhage. Hematoxylin and eosin; reduced about 35% from mag. × 125.

Comment

The pharmacologic evidence for iproniazid hepatotoxicity is suggestive but inconclusive. Its parent compound, hydrazine, at one time enjoyed considerable popularity as a reliable research tool for the experimental production of hepatic injury in animals.[7] The ability to produce liver damage was demonstrated for a number of hydrazine derivatives as well.[7,8] More recent studies by McKennis et al.[9] indicate that iproniazid, as well as isoniazid, shares this property with their sister hydrazine derivatives. These authors produced fatty livers in rabbits by administering large doses of iproniazid (207 mg. per kilogram). Hepatic damage in other species at lower dose levels, however, is less evident. Rats given the drug at concentrations of 5, 20, and 80 mg. per kilogram for 13 weeks showed evidence of slight parenchymatous degeneration of the liver only with the high doses.[10] Chronic toxicity studies in dogs revealed only slight alterations in gross appearance of the liver with a dose of 3.5 mg., although these changes were moderate and severe at dose levels of 7 and 14 mg., respectively.[10] A single rhesus monkey, given 7 mg. of iproniazid per kilogram daily for 8 days, followed by 14 mg. per kilogram for 10 days, and then 18 mg. per kilogram for 12 weeks, did not reveal any histologic evidence of liver damage when killed.[11]

Although the possibility of potential hepatotoxicity was anticipated on the basis of animal studies, the reports of almost all investigators who employed iproniazid in the therapy of human tuberculosis were reassuring. Notwithstanding transient alterations in liver-function tests, observed in 9 of 52 patients in one series,[12] and transient abnormal sulfobromophthalein retention in 3 of 30 patients in another group,[5] overt jaundice did not occur in large groups of patients treated with the drug.[5,13-15] When jaundice did occur, it was attributed largely to coincidental viral hepatitis rather than drug toxicity. Of 4 cases of jaundice observed during the course of iproniazid therapy in a group of 142 cases of bone and joint tuberculosis,[16] at least 2 were attributed to coincidental infectious hepatitis and 1, to extrahepatic biliary obstruction. In a group of 21 patients with nontuberculous bone and joint infections,[17] 3 other cases developed liver dysfunction while receiving iproniazid. Two of these patients were jaundiced. Again, none was attributed to iproniazid toxicity. In one of these patients with previously diagnosed Laennec's cirrhosis, the development of jaundice was attributed to homologous serum hepatitis. In the other two, hemolytic jaundice due to recent blood transfusions could not be ruled out. Our review of the rather extensive clinical experience gained in the therapy of tuberculosis with iproniazid failed to reveal a single reported case of jaundice attributed to drug toxicity. Dawson and Sherlock,[18] interestingly enough, employed the drug in a group of patients with known liver disease. Although the ability of iproniazid to inhibit amine oxidase apparently resulted in the lowering of blood ammonium levels in 13 of 17 patients in their study, 1 lapsed into hepatic coma. As a result of this, the authors concluded that the drug was not indicated in the therapy of hepatic coma because circulating amines may be more toxic to the brain than ammonium. The possibility of other unknown metabolic effects of iproniazid in the one case that deteriorated was also considered. As late as December, 1957, at which time a symposium on iproniazid therapy was held in New York City,[19] jaundice or significant liver dysfunction was not included among the complications of iproniazid therapy.

Only recently have cases similar to our own been reported, in which iproniazid is clearly implicated as the cause of jaundice in patients receiving the drug.[20-24] Some pertinent features of these 18 cases, all reported since January, 1958, are summarized in Table 2 along with our own cases (excluding Case 5).

TABLE 2.—*Twenty-Two Reported Cases of Jaundice Associated with Iproniazid Therapy*

Authors	Cases, No.	Age Range	Sex M	Sex F	Daily Dose Range, Mg.	Duration of Treatment Prior to Jaundice, Wk.	Total Dose Range, Gm.	Deaths
A. Cases Developing Jaundice During Initial Course of Therapy								
deVerteuiel & Lehmann [20]	1	--	0	1	50-100	<2	<0.70	1
Zetzel & Kaplan [21]	4	32-75	0	4	25-150	6-9	1.095-9.45	1
Smarr, et al. [23]	2	--	?	1	50-150	5-12	3.25-6.75	1
Frantz [18]	1	47	1	0	100-150	9	8.0	1
Kahn & Perez [24]	7	49-74	1	6	25-150	3-12	0.65-7.35	1
Felix, Schwartz, & Rifkin	4 *	48-68	2	2	50-200	4-8	3.0-9.0	1
B. Cases Developing Jaundice During Second Course of Therapy — Data of Second Course								
Zetzel & Kaplan [21]	1	39	0	1	75	4 days	0.3	0
Kahn & Perez [24]	2	68-82	0	2	25-100	9-14 days	0.6-1.1	1

* Case 5 of this report not included.

The daily dose level in the 22 cases tabulated ranges from 25 to 200 mg. The duration of therapy prior to the appearance of jaundice in the patients receiving a single course of therapy varies from a minimum of 2 to a maximum of 12 weeks, and the total cumulative dose from 0.65 to 9.45 gm. Three patients [21,24] developed jaundice only during a second course of treatment. The duration of therapy prior to jaundice in the second course varied from 4 to 14 days, and the cumulative dose, from 0.3 to 1.1 gm.

The duration of significant hepatic dysfunction in the nonfatal cases was very prolonged, ranging from 5 to 12 weeks. Death occurred in seven cases after a period of jaundice lasting from one to five weeks. Symptomatology was minimal in almost all nonfatal cases. The usual absence of fever is particularly striking. The period of severe hepatic failure uniformly preceding death in the fatal cases was usually sudden in onset and unheralded by significant prodromal symptomatology.

Chemical studies in all cases revealed evidence of liver-cell injury. Kahn and Perez [24] cite two cases, however, in which transient "obstructive" chemistries were observed at the height of jaundice, leading to surgical exploration in one. For the most part, elevations of cephalin flocculation, thymol turbidity, and serum glutamic oxalacetic levels closely paralleled the severity of jaundice and the clinical course. A striking exception was Case 2 of this report, a fatality, whose transaminase levels continued to fall despite rapid clinical deterioration during the final three days of life. All other laboratory studies, aside from liver-function tests, were usually noncontributory. The presence of eosinophilia noted in our first case was not noted in any of the other cases.

Histologic material was available for study in 10 cases (Case 5 included). In three of these, liver biopsy consistently revealed evidence of diffuse hepatitis. In seven cases, autopsy consistently showed evidence of widespread hepatic necrosis. The pathologic changes noted, for the most part, were similar to those seen in viral hepatitis.

All of the patients reported were treated with the usual measures for hepatitis, including bed rest, dietary measures, vitamins, and often antibiotics. Twelve patients received corticotropin (ACTH) or steroid therapy. In none of these could any definite improvement be attributed to the use of hormones.

The single case reported by deVerteuil and Lehmann [20] was one of a group of 31 psychiatric patients treated with iproniazid,

and the 2 cases reported by Smarr et al.[22] occurred in a series of 25 depressed patients treated with the drug. All the other cases represent isolated instances apart from any series or group study.

Many of the consistent findings in the cases available for study allow for some tentative conclusions regarding the nature of iproniazid jaundice. The jaundice associated with iproniazid therapy is clearly hepatocellular in origin and results from a diffuse hepatitis difficult to distinguish from viral hepatitis on clinical as well as histologic grounds. Lacking specific chemical or histologic features, the diagnosis of iproniazid hepatitis must, of course, be circumstantial. It is our feeling that the diagnosis is justifiable in any case of hepatocellular jaundice developing during the course of iproniazid therapy or within two weeks after cessation of therapy in the absence of positive evidence for viral hepatitis or exposure to other known hepatotoxic agents. As noted, jaundice has occurred over a wide range of dose levels. Whether or not the total cumulative dose given, rather than the daily dose level, is significant in determining the onset of jaundice is not clear. Evidence of liver-cell injury and jaundice usually occurs only after two weeks of therapy and is commonly delayed for several weeks. Jaundice occurred earlier in three patients receiving a second course of treatment. The degree of liver damage noted may vary from only mild, transient alterations of liver-function tests to overt jaundice and potentially fatal, widespread hepatic necrosis and hepatic coma. The occurrence of 7 deaths clearly attributed to hepatic injury (Case 5 excluded) in the 23 cases reported to date is most sobering. No specific therapy is as yet available. The recognized regimens for severe hepatic damage, including steroid therapy, are of equivocal effectiveness.

The incidence of iproniazid hepatitis is difficult to determine. An indeterminate number of cases have undoubtedly been previously attributed to coincidental viral hepatitis. The incidence in two series previously noted, i. e., 1 case in a group of 31 patients and 2 cases in a group of 25 patients, suggests that the risk of jaundice may not be negligible.

The pathogenesis of liver damage due to iproniazid remains obscure. The relationship of iproniazid hepatitis to viral hepatitis, if any, is as yet undetermined. Kahn and Perez[24] suggest that iproniazid jaundice represents a manifestation of hypersensitivity. They cite the relative infrequency of jaundice, the lack of correlation with dose levels, and the shorter period of time prior to the development of jaundice in patients receiving a second course of therapy as evidence for this. The possibility of direct chemical hepatotoxicity cannot be disregarded, however. The action of iproniazid as a potent inhibitor of amine oxidase,[25] its chemical relationship to hydrazine, and its possible involvement in the metabolism of pyridoxine[26] suggest several possible modes of liver toxicity. The effects of increased circulating amines, the possibility of heretofore unrecognized inhibition of other enzyme systems and of interference in the metabolism of B-complex vitamins all require consideration as possible pathogenetic factors in the production of liver damage by iproniazid.

In view of recent clinical experience, there is little question that iproniazid must be considered a potentially hepatotoxic agent. Although complete abandonment of the drug as an unsafe therapeutic agent is as yet unwarranted, appropriate precautions in its clinical use must be taken. It is probably best to withhold the drug from patients with known liver disease until the effects of iproniazid therapy in such patients are adequately studied. Liver-function studies prior to treatment and at regular intervals during the course of therapy are strongly recommended. Immediate cessation of therapy with the first appearance of any evidence of liver dysfunction seems advisable. Although only minimal effective doses of iproniazid should be employed as a general principle, the occurrence of severe hepatic damage even with very

low dose levels militates against the possibility of eliminating this unfortunate complication by the employment of lower doses.

Summary

Four cases of hepatocellular jaundice developing in patients receiving iproniazid and attributed to drug toxicity are presented. A fifth case is presented in which a nonjaundiced patient, dying of probably unrelated causes, showed widespread focal necrosis of the liver at autopsy, attributable to iproniazid therapy.

The literature concerning iproniazid jaundice is reviewed, and the pharmacologic and clinical evidence relative to the ability of iproniazid to cause hepatic damage is discussed.

The clinical features of 18 other cases reported in the recent literature of jaundice occurring in the course of iproniazid therapy are summarized.

It is concluded that liver damage as a complication of iproniazid therapy is a very real and life-threatening danger. Appropriate precautions in the clinical use of the drug are recommended.

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Abnormal Hepatic Tests in Muscular Disease

Preliminary Report

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Introduction

Many clinical observations relating liver function to muscle disease have not been objectively tested.[1-3] The observation that some patients with muscular disease have had episodes of jaundice suggested a study of liver functions in patients with muscular disease.

Material and Methods

1. *Test Selection.*—Since few tests measure hepatic function directly, the term "hepatic test" is preferable to "liver-function test." Abnormal findings are often registered without significant alteration of hepatic structures. Contrariwise, almost all hepatic tests yield normal values in approximately 10% of patients in whom abnormalities should be expected.

A fusion of clinical and experimental results is needed before liver function may be analyzed accurately in terms of measurable components. Some writers claim that only sulfobromophthalein (Bromsulphalein) and urinary coproporphyrin are unequivocally significant independently.[4] Tests which appear to represent different functional changes actually are consequences of a common set of factors; therefore, a large battery of tests is superfluous.

2. *Composition of Test Group.*—From a group of 254 patients with neuromuscular disease, 66 were selected, as listed in Table 1. These all had the following tests: cephalin flocculation, thymol turbidity, sulfobromophthalein retention, total protein, albumin-globulin ratio, total cholesterol, and fasting blood sugar. The abbreviations and normal values for these tests, as well as certain other data to be found in other tables, are given in Table 2. Liver biopsies were done in 22 of the 66 "hepatic test" patients.

Submitted for publication Sept. 9, 1958.

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TABLE 1.—*Composition of Patient Group*

Disease	No. Patients	Mean Age
Myasthenia gravis	6	39
Progressive muscular weakness	4	32
Pseudohypertrophic muscular dystrophy	5	14
Myopathy, cause unknown	10	33
Progressive muscular dystrophy	16	26
Wilson's disease	2	
Paramyotonia congenita	1	42
Dystrophia myotonica	7	36
Charcot-Marie-Tooth	1	28
Polyneuropathy	1	46
Progressive muscular atrophy	3	43
Amyotrophic lateral sclerosis	3	43
Friedreich's ataxia	2	40
Hereditary cerebellar ataxia	1	32
Polyarteritis nodosa	1	47
Scleroderma	1	50
Dermatomyositis	1	40
	—	—
Total	66	35

TABLE 2.—*Legend of Abbreviations*

Symbol	Meaning	Normal Values
L	Liver enlarged	2 fingerbreadths enlarged
J+	Jaundice by history	Frank scleral or integumentary
TP	Total protein	6.7-8.2 gm. % (Biuret)
A/G	Albumin/globulin	50%-70% of total difference gm. % or 1.00 in these studies (Dye)
FBS	Fasting blood sugar	65-110 mg. % (Nelson-Somogyi)
Chol. total	Cholesterol	150-250 mg. % (Abell)
CF	Cephalin flocculation, 24 hr.	0-1+ (Hangar)
TT	Thymol turbidity	0-4 Shank-Hoagland units (McLagan)
BSP	Sulfobromophthalein excretion	0%-4% retention 45 min. (Goebler)
AP	Alkaline phosphatase	0.8-2.9 BL adults 2.8-6.7 BL children (Bessy, Lowry & Brook)
Bilirubin T/D	Total direct	0.1-1.1 mg. % 0.06-0.25 mg. % (Malloy & Evelyn)
Uro.	Urobilinogen	0-1.0 Ehrlich units (Watson)
Hx	History of	
BMR	Basal metabolic rate	−15 to +15
PBI	Protein-bound iodine	3.4-8.0μg. %
ESR	Erythrocyte sedimentation rate	M/O-18 mm/hr. F/O-20 mm/hr.

The following tests, which reflect more accurately the degree of bile flow interference, were done in the same 22 patients and in the controls (see below): alkaline phosphatase, total and direct-reacting bilirubin, urinary quantitative urobilinogen.

3. *Diagnostic Criteria.*—There is no unanimity of opinion regarding the criteria of diagnosis of the diseases of muscle. Some of the fundamental reactions of muscle to disease, and the clinical entities with which these reactions are associated have been well described by Greenfield et al.[18] and form the basis for the clinical classification used in this study. It is as follows:

1. Distal muscular syndromes (excluding myotonic syndromes).
   (*a*) Neurogenic (neuropathies): The small muscles of the hands, feet, forearms, and legs are earlier and more severely affected than other muscles. Independent evidence includes fasciculation, Babinski sign, sensory disturbances, muscular wasting.
      (1) Amyotrophic lateral sclerosis.
      (2) Sensorimotor peripheral neuropathies.
   (*b*) Possibly neurogenic (definite patterns of wasting).
      (1) Motor peripheral neuropathies.
      (2) Anterior muscle compartment syndromes of lower extremity (either proximal and/or distal).

Pathological changes in this group include large groups of small muscle fibers (smaller than 20μ diameter), enlargement of nucleoli, and relative increase in muscle nuclei.

2. Myotonic syndromes.
   (*a*) Dystrophia myotonica.
   (*b*) Myotonia congenita.
   (*c*) Paramyotonia congenita.

Pathological changes include ringed fibers, sarcoplasmic masses, and internal nuclei.

3. Proximal muscle syndromes (myopathies): The muscles of the pectoral and pelvic girdles are affected earlier and more severely than other muscles. These include muscular dystrophy and myositis.
   (*a*) Clinically, the onset may be in childhood and adolescence (long duration, with or without sibling or blood relative involvement, and no inflammation) or after 40 years of age with no family history of similar illness. There is wasting, waddling gait, myopathic facies, and hyporeflexia. Enlarged muscles in children are not necessarily due to fat deposition but may represent true hypertrophy, with fiber diameters of 50μ-107μ.
   (*b*) Pathological changes include abnormally large fibers (100μ-150μ), structural changes, phagocytosis of fibers, internal nuclei, basophilic fibers with vesicular nuclei and prominent nucleoli, leukocytic infiltrations, and abnormal endomysial collagen and fat.
4. Myasthenia gravis.
   (*a*) Clinical.
      (1) Weakness and easy fatigability most commonly in muscles innervated by cranial nerves.
      (2) Relieved by anticholinesterases (neostigmine).
   (*b*) Pathological changes.
      (1) Leukocytic infiltration (lymphocytes) about small vessels and adjacent to normal muscle fibers.
      (2) Presence or absence of plasma cells and histiocytes.

4. *Composition of Control Group.*—The controls were 40 ophthalmological and neurosurgical patients with no history or objective findings of neuromuscular disease. Thirty-five were white; five, Negro; one, red; eighteen, male, and twenty-two, female. Age ranged from 6-60 (mean, 33). Expressed as percentages of the total number of controls, the incidence of hepatic test abnormalities is as follows:

	%
Albumin-Globulin	33
Total protein	28
Cephalin flocculation	10
Cholesterol	5
Urobilinogen	5
Thymol turbidity	5
Sulfobromophthalein	3
Alkaline phosphatase	3
Bilirubin	0

The mean number of abnormalities per patient for 10 hepatic tests was 1.00. The frequent (33%) occurrence of abnormal albumin, globulin, or A/G ratio in this group remains unexplained.

5. *Analysis of Results.*—To save space results have been tabulated only for diseases with significant derangements. For each patient the number of abnormal hepatic tests is enumerated, as well as the incidence of abnormal values for each of the tests. These abnormal incidence values are expressed as a per cent of the number of patients in that group having the test in order to determine the frequency of derangement of a particular test for each disease. That mean number of abnormal tests per patient is statistically compared with the same value (1.00) for the control group as an index of over-all disturbance of tests. Each of the abnormal test means (mean number of abnormal values for each test) is then compared with the control group in order to determine for a particular disease which tests, if any, are most frequently abnormal.

TABLE 3.—*Proximal Muscle Syndromes*

Pt.	Age	Race	Sex	CF	TT	BSP	FBS	TP	A/G	Chol.	Biopsy	Remarks	Abnormal Values Pt., No.
1	42	W	F	1	5	6	68	6.3	3.9:2.1	250		L+ fever (hx)	4
2	56	W	M	Neg.	3	2	56	7.4	3.6:3.8	239	Neuropathy severe		2
3	47	W	F	2	4	5	61	7.2	4.1:3.1	309	Muscle "atrophy"		4
4	50	N	F	Neg.	9	3	61	7.5	2.8:4.7	143	None	AP, 1.5; bilirubin, 1.0/2.1 PBI, 1.9 Urobilinog, + 1.3	4
Mean values				0.75	5.3 *	4	61.5 *	7.1	3.6 :3.4	235			3.5
Standard deviations				0.45	2.63	1.82	4.93	0.55	0.57:1.1	68.79			
Incidence of abnormal values for each test				1	2	2	3	1	2	3			
Incidence of abnormal values, % of no. of patients				25	50	50	75	25	50	75			

* Abnormal mean values.

Results

Findings for patients in statistically significant groups are tabulated in Table 7. These will be discussed. Patients with diagnoses of progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, and myopathy of unknown cause, all come under the heading of proximal muscle syndromes in the Greenfield classification. Not all of the patients had the complete profile of seven hepatic tests. Patients with abnormal muscle exhibiting primarily fatty changes are as follows: progressive muscular dystrophy, 5; pseudohypertrophic muscular dystrophy, 4; myopathy of unknown cause, 2; polyneuropathy, 1; dermatomyositis, 1 (total, 13). In this group of 13 patients, 11 patients had the seven-test profile, with a mean of 4.3 abnormalities per patient for the group. Three patients with progressive muscular dystrophy (two of them were sisters) presented increased connective tissue as the basic pathological change in muscle. Liver biopsies (Vim-

TABLE 4.—*Pseudohypertrophic Muscular Dystrophy*

Pt.	Age	Race	Sex	CF	TT	BSP	FBS	TP	A/G	Chol.	Biopsy	Remarks	Abnormal Values Pt., No.
5	30	W	F	Neg.	5	5	67	6.4	2.2:4.2	300	Fat with few muscle fibers	L Cholecystectomy	5
6	15	W	M	2	5	6	60	7.0	3.5:3.5	290	Fatty endomysium	L bro. with J muscle dis. + hx J	6
7	34	W	M	3	5	5	63	7.1	3.5:3.6	234	Myopathy		5
8	7	N	M	2	6	5	64	7.8	3.8:4.0	257	Fatty tissue + muscle fibers		6
9	52	W	M	1	5	5	73	6.5	3.5:3.0	278	Endomysial fatty change	L; splenomegaly; alcohol	
Mean values for each test				1.6 *	5.2 *	5.2 *	65.4	6.9	3.1 :3.7 *	272			5.4
Standard deviations				1.14	0.45	0.45	4.93	0.57	0.66:0.47	26.5			
Incidence of abnormal values for each test				3	5	5	3	2	5	4			
Incidence of abnormal values, % of no. of patients				60	100	100	60	40	100	80			

* Abnormal mean values.

TABLE 5.—*Progressive Muscular Dystrophy*

Pt.	Age	Race	Sex	CF	TT	BSP	FBS	TP	A/G	Chol.	Biopsy	Remarks	Abnormal Values Pt., No.
10	8	W	M	Neg.	2	3	62	7.6	3.9:3.7	187	Normal		2
11	17	W	M	Neg.	2	2	60	7.1	4.1:3.0	129		AP-2.7; bilirubin, 0.2/0.05	2
12	40	W	F	2	5	5	58	6.3	3.1:3.2	241	Neuropathy + myopathy	BMR, −19	6
13	37	W	F	1	6	5	64	5.9	2.3:3.6	277	Neuropathy + myopathy	L, mother with liver & muscle disease	6
14	12	W	M	Neg.	2	2	65	6.2	3.0:3.2	119	Adv. myopathy with incr. conn. tissue	AP-4; $\frac{0.1}{0.06}$ =T/D	3
15	15	W	F	2	3	5	67	6.9	4.0:2.9	146	Myopathy with incr. conn. tissue	J+	3
16	19	W	F	Neg.	3	2	66	6.7	4.0:2.7	163	Myopathy with incr. conn. tissue	AP-1.9	1
17	19	W	F	1	3	2	76	6.9	3.8:3.1	194	Small fibers		1
18	52	W	F	2	5	5	80	6.2	3.3:2.9	253	Fibrofatty changes	Calcification in liver region	6
19	40	W	M	2	6	5	86	6.8	3.6:3.2	267	Fibrofatty changes	High glucose tolerance curve	5
20	56	W	M	2	4	7	58	6.4	4.0:2.4	256	Fatty muscle	Thyr. enl.; J+	6
21	24	W	F	4	4	12	57	6.3	3.4:2.9	164	Fatty muscle	AP, 0.9; J+ (inf. hep.)	5
22	22	W	F	2	4	1	61	7.5	3.7:3.8	149	Myopathy	Infectious hepatitis; J+	4
23	11	W	F	2	5	6	68	7.8	3.6:4.2	195	Myopathy		4
24	13	W	M	2	4	3	73	7.1	4.1:3.0	182	Myopathy		1
25	15	W	F	2	4	5	63	6.5	3.2:3.3	212	Myopathy		5
Mean values				1.5 *	3.9 *	5.7 *	66	6.7	3.6:3.2	196			3.7
Standard deviations				1.1	1.3	2.68	8.37	0.56	0.50:0.37	50.5			
Incidence of abnormal values				10	5	9	8	7	13	8			
Incidence of abnormal values, % of no. of patients				43	14	29	29	49	85	49			

* Abnormal mean values.

Silverman technique) in 22 patients revealed fibrofatty nodules and a bile duct hamartoma in one myasthenic with lymphorrage of the muscles, fatty infiltration in 15 patients (of which 11 were in the abnormal-test group) and no pathological change in the remaining 6. In the group of biopsied abnormal-test patients with fatty infiltration six, or over 50%, had histologic evidence of hepatocellular disease. Only one of these had had infectious hepatitis, which occurred in only three patients in the whole study, although episodes of jaundice were accompanied by fever in 10. The presence of previously undiagnosed infectious hepatitis cannot be ruled out, however. Forty-five (68%) of the sixty-six "hepatic" test patients had myopathies, or myopathy plus neuropathy by biopsy. Four cases which were considered myopathy clinically also had neuropathic changes on biopsy. One case each of Charcot-Marie-Tooth disease, Friedreich's ataxia, and amyotrophic lateral sclerosis unexpectedly had myopathy on biopsy.

Significant differences between mean hepatic test abnormalities in the controls versus test patients were found in progressive muscular dystrophy (16 patients), pseudohypertrophic muscular dystrophy (5 patients), and myopathy of unknown cause (10 patients).

With use of Welch's method with 99% confidence limits, significance can be evalu-

TABLE 6.—*Myopathy of Unknown Cause*

Pt.	Age	Race	Sex	CF	TT	BSP	FBS	TP	A/G	Chol.	Biopsy	Remarks	Abnormal Values Pt., No.
26	37	W	M	1	2	5	64	8.0	4.0:4.0	253	Marked fibro-fatty endomysial change		4
27	37	W	M	3	6	5	57	7.8	4.3:3.5	242	Myopathy with eosinophilic masses		4
28	64	W	F	Neg.	2	3	71	6.6	3.5:3.1	286	Myopathy neuropathy		3
29	16	N	F	Neg.	6	1	59	6.9	3.5:3.4	211	J+; urob, 1.1; T/D, 0.3/0.04	Severe myopathy	3
30	30	W	F	3	14	2	63	7.3	3.3:4.0	105	Myopathy		5
31	70	W	M	4	7	21	64	8.1	4.0:4.1	257	?myopathy ?liver	J+; liver, 0; L, fatty infilt	6
32	49	W	M	Neg.	4	5	61	6.9	3.3:3.6	192	Myopathy marked by endomysial fat	Liver	3
33	37	W	F	2	2	2	85	7.1	3.0:4.1	258	Not reported	Urobilinogen, 1.1; bilirubin, 0.2/0.03; AP, 1.4	3
34	28	W	F	2	5	2	68	7.1	3.5:3.6	263	Myopathy		4
35	61	W	F	2	5	4	66	7.0	2.9:4.1	349	Myopathy	Hx typhoid	4
Mean values				1.7 *	5.3 *	5 *	63.8 *	7.3	3.5:3.8 *	242			4 (out of 7 tests)
Incidence of abnormal values				6	6	4	6	1	6	6			
Standard deviations				1.42	3.56	5.81	8.17	0.51	0.45:0.36	63.84			
Incidence of abnormal values, % of no. of patients				60	60	40	60	10	60	60			

* Abnormal mean values.

ated from a small sample. Out of 254 patients, 36 had had jaundice and/or liver enlargement. The largest incidence of hepatomegaly was in patients with myopathy of unknown cause and progressive muscular dystrophy. Progressive muscular dystrophy patients had the highest incidence of jaundice.

Comment

The incidence of hepatomegaly and jaundice, prime "hepatic tests" in themselves, correlates with the laboratory results. The abnormal tests can be arranged in descending order of frequency for the three significant disease categories, as follows: A/G, sulfobromophthalein retention, thymol turbidity, total cholesterol, cephalin flocculation, fasting blood sugar, and total protein. Sulfobromophthalein retention and thymol turbidity, both of high "significance" in terms of abnormal hepatic function, are more frequently abnormal in the three disease categories which were significantly different from the controls. There was a positive correlation throughout between abnormal sulfobromophthalein and abnormal thymol turbidity.

In the group of myopathies having excessive connective tissue on biopsy, serum cholesterols were consistently low (mean, 142). Where fatty tissue was predominant on biopsy, mean cholesterol was 269 (normal upper limit, 250) and the mean number of abnormalities was also significantly different from the controls. Further, the largest number of patients in this group were those with progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, and myopathy of unknown cause. In the "fatty myopathy" group, 7 out of 13 had jaundice or liver enlargement.

1. *Pathological Correlation Between Hepatic and Muscle Abnormalities.*—The results suggest an association between a

TABLE 7.—*Patients of Total Group (254) with Liver Enlargement, History of Jaundice, or Both*

Liver enlargement	Paramyotonia	1
	Pseudohypertrophic muscular distrophy	2
	Progressive muscular dystrophy	4
	Unknown cause (myopathy)	6
	Myotonia congenita	1
	Wilson's disease	2
	Dermatomyositis	1
	ALS	3
	Choreoathetosis	1
	Polyneuropathy	2
	Myasthenia	2
	Total	25
Jaundice	Progressive muscular dystrophy	6
	Dissem. lupus erythematosus	1
	Pseudohypertrophic muscular dystrophy	1
	Unknown myopathy	1
	Infantile myopathy	1
	Polyneuropathy	1
	Cerebellar ataxia	1
	Mononeuronitis multiplex	1
	Myasthenia	2
	Total	15
Both	Polyneuropathy	1
	Progressive muscular dystrophy	1
	Pseudohypertrophic muscular dystrophy	1
	Myopathy of unknown cause	1
	Total	4

Gross Index, %

	Liver-Jaundice Group (36 Patients)	Profile Group (66 Patients)	Sample (254 Patients)
Liver enlargement	69	38	10
Jaundice	41	23	6
Both	11	6	2

generalized systemic disturbance and muscle lesions. The abnormal hepatic test and biopsy results suggest that an episodic or progressive hepatocellular dysfunction has been in process. This may result from fatty metamorphosis, which for want of more precise pathogenetic studies, remains a vague term. In this disorder, sulfobromophthalein retention is the most frequent abnormality. Usually albumin is lower than normal, cephalin flocculation and thymol turbidity may be abnormal, the alkaline phosphatase is elevated, glucose tolerance is lowered, and there is often hypoglycemia (glycogen depletion). With liver-cell degeneration, jaundice ensues. The results of the present study are in agreement with these observations.

The influence of diet on hepatic vitality is tremendous, but its relationship to muscle is complicated. In kwashiorkor, in which there is fatty infiltration of the liver, muscle wasting is "severe."[5] Many animal dietary studies support the hypothesis that liver damage and muscle wasting are associated expressions of a common imbalance. The presence of depressed scars in the livers of dystrophic rats dying of dietary hepatic necrosis[6] may indicate one or more previous episodes of liver-cell degeneration. In the present study 6 (37.5%) of the 16 patients with progressive muscular dystrophy had had unexplained acute episodic jaundice years previously. The acute episode of jaundice preceded the clinical diagnosis of neuromuscular disease in 13 patients (19 had jaundice). This makes it unlikely that hepatic involvement in these patients was related to inactivity or debilitation. Rather, this suggests intrinsic liver damage, related to the primary disease process. From the case histories nothing definite can be said regarding the general condition of the patients with abnormal tests as compared to that of the others.

This is a difficult matter to resolve. For example, pseudohypertrophic muscular dystrophy in which there is a high incidence of abnormal hepatic tests, occurs in younger, ostensibly more vigorous, persons. Nevertheless, it is a more violent and rapidly moving process than "myopathy of late onset," which is often clinically mild.

2. *Biochemical Relationships Between Hepatic and Muscle Abnormalities.*[7]—Fatty metamorphosis leads to fibrosis, bile stasis, and hepatocellular damage. The ways in which such lesions could affect muscle involve numerous biochemical relationships, affecting lipids, carbohydrates, and amino acids, especially sulfo-methylamino acids. It would be crucial to demonstrate that the lipid which is found in the fatty deposits of dystrophic muscle is the same as that abnormally stored in the liver.

Hove et al.[8] described choline deficiency in the rabbit, including anemia, *fatty and cirrhotic livers*, necrosis of kidney tubules,

creatinuria, and *"progressive muscular dystrophy."* Monomethyl-amino-ethanol and methionine together protected the animals.

3. *α-Tocopherol.*—α-Tocopherol deficiency results in muscular dystrophy in cattle, lambs, and pigeons, and possibly in humans, although there is no apparent human counterpart to the neuromuscular disorder seen in animals with vitamin E deficiency. When given parenterally to dystrophic animals, vitamin E has no effect. When given orally, recovery occurs, indicating that the antidystrophic principle is formed by conjugation or some other change. In liver diseases Klatskin found low plasma α-tocopherol values.[10] Decreased activity of liver enzymes associated with a low-protein diet was partly ameliorated by vitamin E.[11] Rats fed hepatotoxic substances showed decreased tocopherols in body lipids[12] and were protected by vitamin E.[13]

4. *Endocrine Changes.*—Mortality due to liver necrosis in experimental animals is less in females, which have a higher incidence of muscular dystrophy than males.[14]

Conclusion

These results allow one to *reject* the hypothesis that, in this preliminary study, patients with progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, and "myopathy of unknown cause" have normal hepatic tests as compared with a control group. Stated in terms of the confidence limits, the probability that the difference between these categories and the control is due to chance is 1 in 100.

Summary

A series of hepatic test results on 66 patients with neuromuscular disease is reported.

Abnormalities were found to be significantly different from controls in biopsy-proven progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, and myopathies of unknown cause.

These abnormalities, found only in patients with proximal muscle syndromes, may represent the hepatic manifestation of a generalized systemic disturbance in such diseases. Abnormalities in hepatic tests assumed a pattern suggestive of fatty metamorphosis. Liver biopsies in 15 patients revealed fatty infiltration.

Some metabolic mechanisms are mentioned including liver-muscle interrelationships concerning lipid and sulfo-amino acid balance, creatine balance, methyl-group balance, α-tocopherol metabolism, and endocrine activity.

At present no correlations can be made between fatty infiltration of the liver and fat deposits in endomysium.

Miss Mary R. Shepard assisted with the statistical analysis.

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Case Reports

The Syndrome of Acute Disseminated Moniliasis in Adults

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Most infections of infancy and childhood are not encountered in adults because of the immunity acquired through repeated or constant exposure to the responsible micro-organism. Under unfavorable conditions, however, adults may regain their susceptibility to certain childhood pathogens, as illustrated by the relatively high incidence of disseminated tuberculosis and histoplasmosis in older adults,[1,2] by the systemic Hemophilus influenzae infections of alcoholics,[3] and by the generalized form of herpes zoster (resembling chickenpox) in leukemia.[4] Another childhood infection [5-13] that has been observed only rarely in adults is disseminated moniliasis.

Because of the recent emphasis placed on the problem of Candida infections in adults an attempt has been made to define the clinical syndrome of systemic moniliasis and to determine the disturbance in resistance responsible for such infections in adults. This has been done by analyzing the manifestations of the disease observed in the present case report, as well as those described in the few cases reported previously.

Report of Case

Clinical Summary.—A 55-year-old white man was transferred to the Presbyterian Hospital on Aug. 15, 1957. After dinner on Aug. 3, he suddenly experienced epigastric discomfort, nausea, and severe vomiting. An x-ray of the abdomen demonstrated only gas-filled loops of small intestine. His complaints and physical findings were confined to the abdomen, which was distended and tender to deep epigastric pressure. Peristalsis was slow, and there were no palpable organs or masses. The white blood cell count was 12,550, and the blood urea nitrogen was 30.9 mg. %. A Miller-Abbott tube was inserted, and during the next three days it progressed satisfactorily into the jejunum. His condition remained unchanged after a week of conservative treatment, and an exploratory laparotomy was performed through a small right-lower-quadrant incision. The peritoneal sac contained abundant clear, straw-colored fluid. A noninflamed Meckel's diverticulum was discovered, and the bowel proximal to this was greatly dilated and somewhat dusky. In mobilizing the Meckel's diverticulum the ileum was penetrated accidentally. The diverticulum, together with a few centimeters of proximal and distal ileum, was resected, and a double-barreled ileostomy was performed. Escherichia coli was cultured from the abdominal fluid, and the patient was treated orally with chloramphenicol and neomycin.

Although his abdomen was still distended, he was brought to the operating room four days later for anastomosis of the ileum. A small abscess was discovered between the proximal ileostomy and the skin. This was drained, and nothing further was done, since his systolic blood pressure had fallen to 70 mm. Hg. Levarterenol (*l*-norepinephrine) was used to maintain an adequate blood pressure, and he was transferred to the Presbyterian Hospital in Pittsburgh. On admission to the Presbyterian Hospital, he was markedly dehydrated, confused, and had a temperature of 103.4 F rectally. Although peristalsis was still depressed, the abdomen was now soft and tender only about the ileostomy.

Initial laboratory studies, summarized in Figure 1, demonstrated that the patient was suffering from hyperglycemia, hypocalcemia, hyperphosphatemia, and azotemia. X-rays demonstrated an elevated right hemidiaphragm. Intravenous fluid and electrolyte therapy were directed toward the correction

Submitted for publication Oct. 13, 1958.

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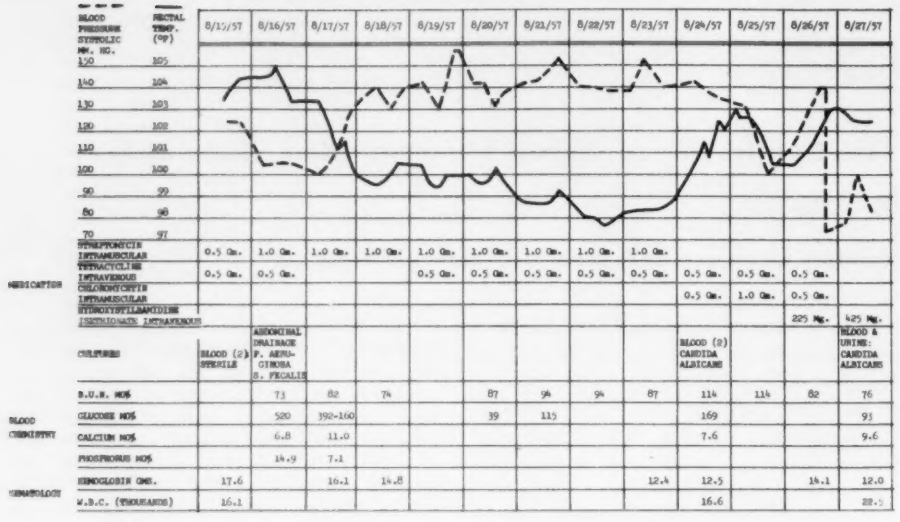

Fig. 1.—Summary of initial laboratory studies.

of the markedly impaired fluid and electrolyte balance. Antibiotic therapy consisted of 0.5 gm. of tetracycline intravenously for the first two days and 0.5 gm. of streptomycin intramuscularly twice daily. Two blood cultures at the time of admission were sterile, while cultures of the abscess about the proximal ileostomy site revealed Pseudomonas aeruginosa and Streptococcus faecalis but no C. albicans. The P. aeruginosa was resistant to all antibiotics except polymyxin B in high concentrations. A Levin tube was inserted and connected to Wagensteen drainage. There was considerable gastric drainage during the first three days, and the daily urine output remained below 300 ml. On the fourth day the urinary output began to increase, and a serum amylase done then was 470 Somogyi units. Large doses of calcium gluconate temporarily corrected the hypocalcemia, but the prodigious use of intravenous fluids and electrolyte solutions failed to correct the elevated serum phosphorus and blood urea nitrogen.

During succeeding days the urinary output gradually increased, and the specific gravity became fixed at 1.010. The Levin tube was removed, and small quantities of liquids were given by mouth. On the fifth day a localized phlebitis developed about a cut-down site on the left leg, and the patient intermittently vomited small quantities of bile-stained fluid. In addition to the streptomycin, 0.5 gm. of intravenous tetracycline was given daily.

Although the temperature had returned to normal on the fourth day, by the eighth day the patient was drowsy and nauseated. Scleral icterus was noted and the Levin tube was reinserted. Early on the tenth day he became stuporous, his temperature began to rise, and small quantities of blood were recovered from the Levin tube and proximal ileostomy. He was hyperpneic, and, since the phlebitis on the left leg had increased, it was feared that a pulmonary embolism had occurred. The streptomycin was stopped and replaced with 0.5 gm. of intramuscular chloramphenicol twice daily. Two blood cultures taken the next day contained such heavy growth of C. albicans that the colonies were too numerous to count in the agar plate poured with 1 ml. of his blood. Brief periods of apnea were noted, and he was placed in an oxygen tent. Whole blood, 1,000 ml., and hydrocortisone, 200 mg., were given intravenously. He remained stuporous, his retching became more severe, and the BUN reached 114 mg. %. The following day he was dialyzed on an artificial kidney for 380 minutes. At the end of the dialysis the BUN was 76 mg. %, but the serum potassium had increased to 7.7 mEq. per liter, and the serum calcium remained depressed. Following the dialysis, 225 mg. of hydroxystilbamidine isethionate (Merrell) was given in a slow intravenous infusion. Four hours later his systolic blood pressure fell to 72 mm. Hg, and whole blood transfusions and infusions of arterenol (norepinephrine) were instituted. At this time, both the blood and urine cultures yielded C. albicans. His respirations became shallow and labored, and Cheyne-Stokes breathing ensued. He became comatose, and, despite progressively larger doses of levarterenol during the next 24 hours, the shock proved irreversible and he died.

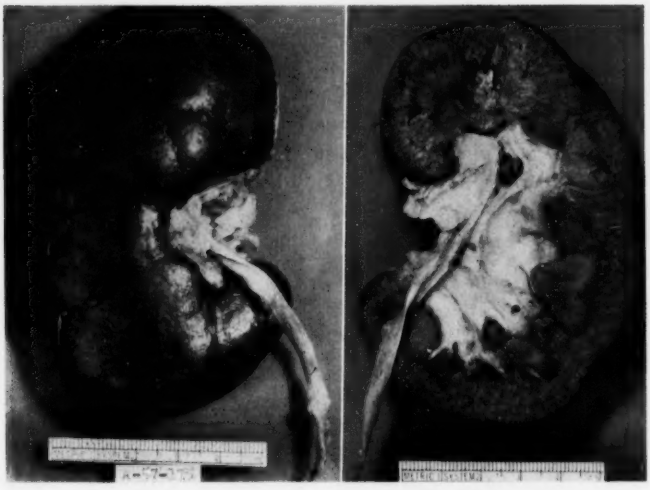

Fig. 2.—The left kidney is studded with numerous discrete mycotic abscesses. There is an area of hemorrhage in the pelvis.

Autopsy Findings.—At autopsy there was 150 ml. of blood-stained fluid in the peritoneal sac. Two centimeters from the resection edge of the proximal loop of ileum there was a rounded perforation of the bowel which communicated with the abdominal cavity. Adjacent to this there was an abscess measuring 2.5 cm. and containing a small amount of yellowish-green purulent material completely encased by mesentery. The serosal surfaces of the entire intestinal tract were glistening grayish-tan; there was no evidence of compromised circulation. Throughout the mucosa of the proximal portion of ileum, jejunum, and duodenum, there were hyperemic foci and numerous small submucosal hemorrhages. Numerous irregular shallow ulcers averaging 1.5 cm. in diameter were also noted in the stomach. The heart weighed 480 gm. and exhibited numerous gray-tan abscesses measuring 0.5 mm. throughout all areas of the sectioned myocardium. The kidneys each weighed 175 gm., and their surfaces were studded by numerous small, elevated, bright gray-tan abscesses, as well as focal areas of hemorrhage. The abscesses were also present on the cut surface and involved the cortex as well as the medulla (Fig. 2). The pelvis of each kidney contained small quantities of blood, and the pelvic mucosa was hemorrhagic. The thyroid weighed 25 gm., and throughout the parenchyma there were numerous small, single and conglomerate gray-tan abscesses (Fig. 3). The right adrenal weighed 25 gm. and the left 15 gm. The adrenal medullas were markedly hemorrhagic. The brain weighed 1,330 gm., and, although the meninges and external surfaces were not remarkable, multiple coronal sections through the cerebral hemispheres revealed an elongated, hemorrhagic mass of soft necrotic tissue involving the left globus pallidus, the putamen, the internal capsule, the external capsule, and the claustrum. Numerous petechiae averaging less than 0.1 cm. in diameter were noted throughout the remaining sections of the cerebrum, the pons, the cerebellum, and the brain stem. The pancreas was firm, and throughout the parenchyma there were numerous small irregular firm dark-yellow areas. The pancreatic duct was patent. The liver weighed 2,200 gm., and the cut surface bulged, but it was otherwise not remarkable.

Fig. 3.—The mycotic abscesses in the thyroid are larger than in the kidney and many coalesce.

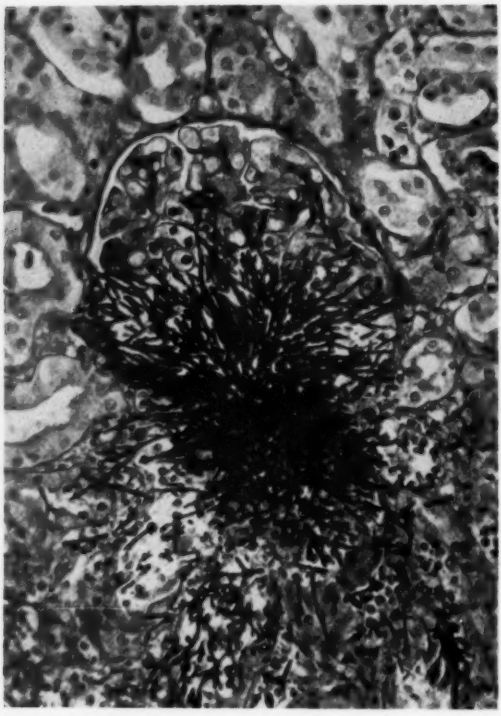

Fig. 4.—Photomicrograph of a glomerulus infiltrated and partly replaced by the dense growth of C. albicans. The yeast form predominates at the periphery in the absence of phagocytosis. Hematoxylin and eosin; × 300.

Microscopic Findings.—Multiple mycotic abscesses were found in the kidneys, heart, thyroid, brain, pancreas, adrenals, and liver. In the kidneys the round abscesses involved all areas of the parenchyma and produced complete replacement of some glomeruli, plugging of some tubules, and numerous interstitial nodues, which distorted adjacent tubules. In the center of these abscesses

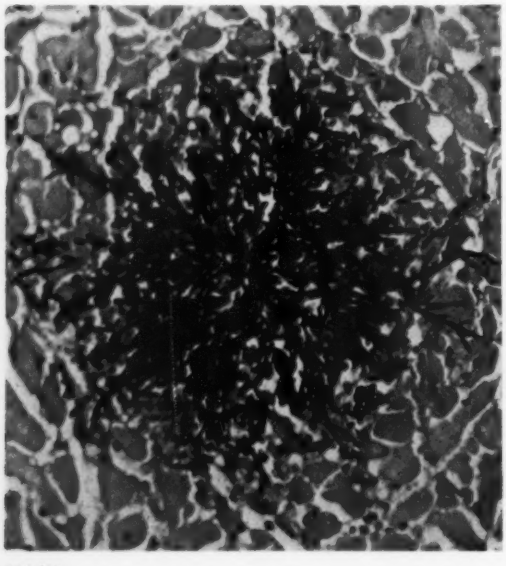

Fig. 5.—Photomicrograph of C. albicans in the myocardium. Hematoxylin and eosin; × 300.

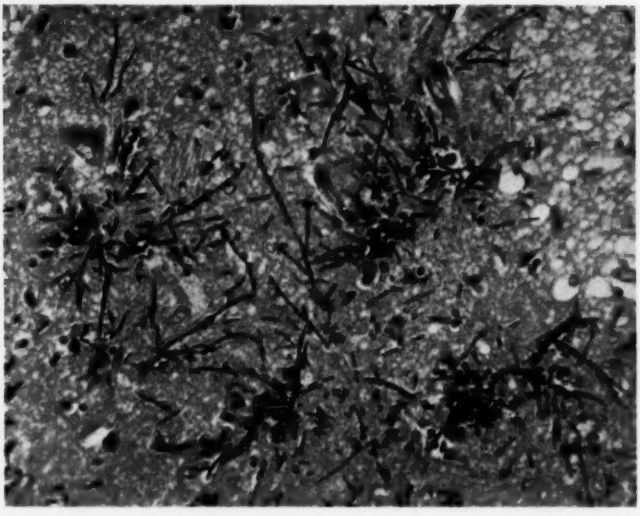

Fig. 6.—Photomicrograph of the cerebral cortex. The fungal masses are smaller and less dense than in the other organs. Note the sparse cellular reaction. Hematoxylin and eosin; reduced about 10% from mag. × 300.

renal cells were frequently destroyed, and the few remaining organisms were in the hyphal form. Toward the periphery there were dense, tangled masses of hyphae and spores. The yeast form predominated at the edge where there were numerous segmented leukocytes and some lymphocytes, macrophages, and plasma cells. Phagocytosis was not observed in any of the sections (Fig. 4).

The myocardium was diffusely involved with many rounded abscesses similar to those in the kidney. Here, too, the yeast form was prominent at the periphery where the inflammatory reaction was most intense (Fig. 5).

In the thyroid the abscesses were not rounded but extended outwardly in all directions. The character of the tissue reaction was similar to that in the kidney, except within the colloid, where the mycelia proliferated in the complete absence of inflammatory cells.

The abscesses were generally smaller in the brain, and there was little cellular reaction (Fig. 6). Many of the abscesses were subcortical and in one instance had almost ruptured into the subarachnoid space.

Aside from the few mycotic abscesses in the pancreas there were numerous areas of fat and

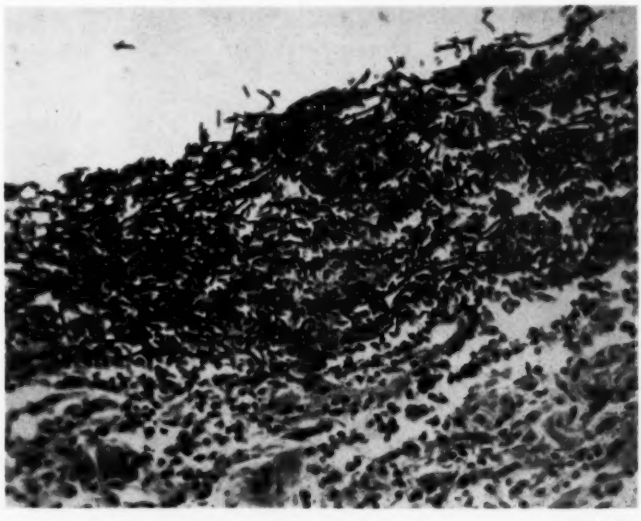

Fig. 7.—Photomicrograph of a superficial ulcer in the ileum. The mucosa is replaced by tangled masses of hyphae and leukocytes. Hematoxylin and eosin; reduced about 10% from mag. × 280.

Analysis of Present Case and Those Reported in the Literature *

Case No.	Authors	Age	Sex	Initial Disease	Length Illness, Days	Culture of C. Albicans from Blood, Days After Onset	Therapy Directed at C. Albicans	Antibiotics	Clinical Features	C. Albicans Cultured	Mycotic Abscesses Observed, Organs
1	Braude & Rock	55	M	Acute pancreatitis	24	21	Hydroxystilbamidine isethionate I. V.	Streptomycin, 1.0 gm. I. M. 8 days; tetracycline, 0.5 gm. I. V. 9 days; chloramphenicol, 1.0 gm. 3 days	Coma, shock, fever, gastrointestinal bleeding, hypocalcemia	Blood, kidneys, lung, spleen, spinal fluid	Kidneys, heart, brain, pancreas, adrenals, thyroid, liver
2	Schaberg, Hildes, & Wilt [14]	22	F	Poliomyelitis & pneumonia	26	23	None	Penicillin, 500,000 units I. M. 21 days; oxytetracycline, dose? streptomycin, 1.0 gm. I. M. 19 days	Confused, shock, fever, gastrointestinal bleeding	Blood, kidneys, spleen	Kidneys, heart, brain, skeletal muscle
3	Davis, Whitaker, Ding, & Kiefer [15]	29	F	Multiple sclerosis Cesarean section	77	11	"Daraprim" pyrimethomine oral	Penicillin, streptomycin, oxytetracycline, "large doses" 67 days, nitrofurantoin (Furadantin), polymyxin, "large doses," 30 days	Coma, shock, fever, gastrointestinal bleeding	Blood, heart, kidney, liver, lung, adrenals, spleen, uterus, pelvic thrombus	Not stated
4	Barrett, Volwiler, Kirby, & Jensen [16]	68	M	Acute pancreatitis	35	31	Nystatin oral	Chloramphenicol, 1.5 gm. I. M. 11 days; tetracycline, 0.4 gm. I. V. 10 days	Confused, fever, rapid decline	Blood, kidneys, pancreas	Kidneys, heart, pancreas

* The case of Van Buren [18] is omitted from the table because the clinical description of the systemic illness and the postmortem cultural findings are incomplete.

acinar necrosis infiltrated with segmented leukocytes and lymphocytes. Many of the acini and all of the major ducts were dilated and contained inspissated secretion.

Multiple sections of the small intestine showed many superficial ulcers containing tangled hyphae and segmented leukocytes (Fig. 7).

In addition to the scattered mycotic abscesses in the liver there was marked central congestion, bile stasis, and fatty metamorphosis. Despite the fact that C. albicans was cultured from the lungs, no organisms were seen in the tissue sections.

Microbiological Examinations.—All cultures, including the antemortem blood and urine cultures, the postmortem cultures of the spinal fluid, the lungs, kidneys, and spleen yielded C. albicans. The identification of C. albicans was established by the production of typical chlamydospores on cornmeal agar and the fermentation of glucose and maltose to acid and gas and of sucrose to acid only. Lactose was not fermented.

The growth of the organism in tryptose broth was prevented in 24 hours by concentrations of hydroxystilbamidine isethionate exceeding 15.6μg. per milliliter and partially inhibited in concentrations as low as 0.9μg. per milliliter. By streaking these cultures on blood agar plates fungicidal effects were noted in concentrations of 31.2μg. per milliliter and greater. Gram stains were made of fungi exposed to each concentration, and, while fewer organisms were present in the smears from the higher concentrations of the drug, no striking morphological changes were noted.

In an effort to determine whether this strain of C. albicans was exceptionally virulent, 0.5 ml. of a 24-hour broth culture was inoculated intraperitoneally into each of four mice, while an equal concentration of a laboratory stock strain of C. albicans was similarly injected into a control group. Only one mouse in each group of four died after the injection.

Analysis of Reported Cases of Acute Disseminated Moniliasis in Adults

This review has been limited to those fatal cases of generalized moniliasis in which the etiology was definitely established by isolation and identification of C. albicans and does not include localized infections of the meninges, lungs, or endocardium. In a review of the literature, surprisingly few cases were found in adults of generalized moniliasis proven at autopsy by culture of the various organs.[14-16] These are described in the Table, which also contains a summary of the features in our case. Fever, shock, mental depression, and intestinal bleeding were the outstanding clinical features of the infection. In three patients, death occurred within five days of the time when C. albicans was cultured. Before the development of the C. albicans septicemia, all patients had received one of the tetracycline antibiotics and three had also been given streptomycin and chloramphenicol. The antibiotics were given in large doses for periods of 11 to 31 days before C. albicans was recovered by blood culture. Pancreatitis was the cause of admission in two of the patients and neurologic diseases in two others.

The main findings at autopsy were mycotic abscesses of the kidneys, heart, and brain. In two patients these abscesses were also observed in the pancreas and in one patient (Case 1) in the thyroid, adrenal, and liver. It is possible that a more thorough search of the thyroid, adrenal, and liver would have demonstrated abscesses in the other patients.

Comment

The syndrome of acute disseminated moniliasis constitutes an entity that can be recognized on clinical grounds alone. There are two outstanding features: (1) a background of continuous antibiotic treatment during the course of a protracted debilitating illness and (2) an abrupt decline in the clinical course with the development of fever, shock, depressed sensorum, and leukocytosis. Gastrointestinal bleeding has also been noted in conjunction with these symptoms.

Culturally proven cases of the disease have been recognized rarely in adults, and no reports could be found in the literature of the preantibiotic era. It is possible, therefore, that antibiotics are a crucial factor in lowering the resistance of adults to a fungus which cannot otherwise establish an overwhelming hematogenous infection, even though it inhabits the bowel of many persons.[17] A partial explanation for the essential action of antibiotics in the development of disseminated candidiasis can be found in

the extensive data showing that C. albicans multiplies excessively in the bowel or mouth if the normal bacterial flora is suppressed.[18-20] But this factor alone cannot account for the development of the disseminated disease because the vast majority of persons with heavy candidal growth in the bowel never exhibit evidence of hematogenous spread. Nor does it seem likely that the antibiotics enhance the virulence of occasional strains, since the strain of C. albicans isolated from our patient possessed no greater virulence in experimental animals than in a standard stock strain.

It is important to emphasize, too, that the strain of C. albicans from our patient had not lost its dimorphic properties. The importance of dimorphism in the pathogenesis of fungus diseases is brought out by the fact that nearly all common systemic mycoses are caused by agents that exist as mycelia in culture media but only in the yeast-like stage in the infected tissues.[21] C. albicans, on the other hand, grows mainly in the yeast form on culture media such as Sabaraud agar but produces abundant mycelia in the tissues. It has been suggested that transformation of C. albicans to the mycelial form in vivo accounts for its low systemic pathogenicity, and it is conceivable that an occasional strain could become more pathogenic by losing the capacity for mycelial transformation.[22] This type of increased pathogenicity through loss of dimorphism from yeast to mycelium has been observed experimentally by Winsten and Murray [23] but was not a factor in the fatal case described in this report because normal dimorphism was evident from the widspread mycelial growth in all tissues.

In considering other factors that permit dissemination after candidal overgrowth of the bowel, one is impressed with evidence of gastrointestinal injury as noted in the patients in the Table. C. albicans is a noninvasive micro-organism that grows profusely in the form of colonies on the surface of mucous membranes without penetrating them. It would seem, therefore, that a hematogenous spread could only develop if this fungus were first provided with a broken area in the mucosa. The occurrence of gastrointestinal bleeding in three of the patients indicates that the mucosa was disrupted, and autopsy examination of our patient did, in fact, reveal multiple superficial intestinal ulcers filled with masses of hyphae and spores.

Hypocalcemia is another finding of possible significance in lowering host resistance to C. albicans. This chemical defect was observed in our patient and possibly in Barrett's patient with pancreatitis.[16] While no values for serum calcium are stated in Barrett's report, hypocalcemia is known to occur frequently in the presence of pancreatitis and is viewed with interest as a potentially related factor in the development of moniliasis. The relationship of hypocalcemia to moniliasis is well established in children with hypoparathyroidism and is thought to be related to the epidermal defects that accompany the metabolic disorder. In adults, however, no connection has been established between hypocalcemia and moniliasis. It is of interest, however, that in sprue, another disease with chronic hypocalcemia, Ashford [25] reported excessive growth of Candida in the bowel.

In contrast to its low invasiveness, C. albicans is capable of serious injury to the host after it has once burst into the circulation and established itself in the tissues. Several of the clinical manifestations can be accounted for by the pathologic processes in the blood and tissues. The prominent cerebral manifestations, which exceed those of most bacterial septicemias, can be clearly related to the predilection of C. albicans for the brain. Similarly, the occurrence of cardiovascular collapse may be a consequence, at least in part, of the numerous mycotic abscesses occurring in the myocardium. It is also likely that the endotoxin of C. albicans contributed to the development of shock, as is the case with bacterial endotoxins in overwhelming septicemias due to Gram-negative bacilli. Salvin,[26] in his experiments in mice, demonstrated endotoxins in all species of Candida and further showed

that the endotoxin of C. albicans was more powerful than the others.

The injury to the infected tissues resulted largely from the mechanical effects of the fungus in the face of relatively slight inflammatory reaction. Even the few inflammatory cells present were impotent against the large, rapidly growing fungal masses as evidenced by the complete absence of phagocytosis. The presence of leukocytes seemed, however, to influence dimorphism in a manner similar to that described in the case of coccidiomycosis.[27] Thus, in the immediate vicinity of the leukocytes, the organism assumed the yeast-like form, whereas mycelial elements predominated where the fungus was not accessible to leukocytes.

Therapeutic efforts seemed futile in the fulminating infection described in the present case report. Nonetheless, an attempt was made to treat the patient with hydroxystilbamidine, because it exhibited partial inhibition of this infecting strain of Candida in concentrations as low as 0.9μg. per milliliter and because it has seemed effective to us in patients treated for pulmonary moniliasis. The drug was not only ineffective, but its use was accompanied by a sharp fall in blood pressure. While the relationship between drug administration and hypotension may have been coincidental, it is possible that Candida endotoxin was released from fungal cells lysed by the drug. Nystatin is another agent capable of inhibiting C. albicans but was not given to this patient because it was not available then for systemic use. This drug is very effective in eliminating Candida from the bowel and has an important place in prophylactic treatment of those debilitated patients who are predisposed to moniliasis through prolonged exposure to antibiotics.[28]

Summary and Conclusions

The syndrome of acute disseminated moniliasis in adults is a definite clinical entity characterized by two outstanding features: (1) a background of continuous antibiotic treatment during the course of a protracted debilitating illness and (2) an abrupt decline in the clinical course with the development of fever, shock, depressed sensorium, and gastrointestinal bleeding.

These clinical manifestations can be accounted for in part by the predilection of Candida albicans for the brain, heart, and kidneys. It is suggested that the severe hypotension may be due to the release of fungus endotoxin from the circulating Candida organisms.

In acute disseminated moniliasis, the lowered resistance to C. albicans is believed to be related to: (1) alteration in bacterial flora of the bowel by antibiotics and (2) injury to the gastrointestinal mucosa.

The possibility that hypocalcemia may be a factor in dissemination of C. albicans is also discussed.

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Sarcoid Heart Disease

A Case with an Unusual Electrocardiogram

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Although sarcoidosis was detailed as a generalized disease by Schaumann,[1] in 1914, early reports placed little clinical significance to well-detailed cardiac lesions.[2-4] Subsequently, evidence of an enlarged heart and heart failure secondary to sarcoid was described in excellent reviews by Longcope,[5] in 1941, and Johnson and Jason,[6] in 1944.

Sudden death from sarcoid heart disease with involvement of the musculature of the left atrium and left ventricle and granulomata adjacent to the coronary arteries demonstrated that this clinical entity could not be regarded as a benign process.[7-9]

The commest electrocardiographic manifestations of sarcoid heart disease previously described included disturbances in rhythm and conduction and prominent P-waves and ST and T-wave changes.[5,6,9-15]

The following case presents for the first time as known to us the findings of Q-waves on the electrocardiogram of a young Negro male patient with generalized sarcoidosis, which was reversible after cortisone therapy.

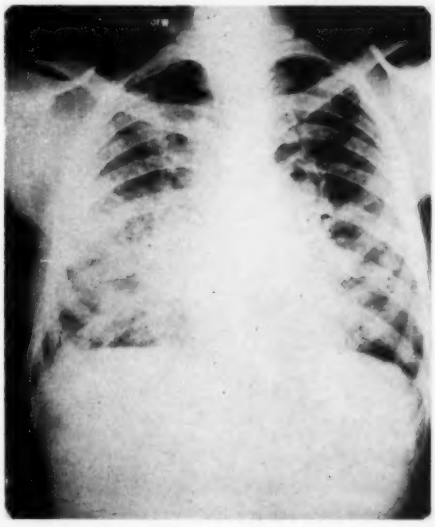
Report of Case

A 24-year-old Negro man was admitted to the Medical Service of Kings County Hospital with a three-months' history of dryness in his throat, productive cough, vague abdominal cramps which were unrelated to meals, and occasional episodes of nausea and vomiting. During this period he also noted increasing weakness, dyspnea on minimal exertion, and a 40 lb. weight loss. His cough became more prominent one month prior to hospitalization and was productive of a copious amount of whitish-yellow mucoid sputum. Hemoptysis was specifically denied. Five days prior to admission he experienced right-sided chest "soreness" and back pain which was aggravated by respiration or cough. He also noted night sweats but did not experience chills or fever.

Past history and family history were noncontributory. Rheumatic fever, tuberculosis, other cardiac, pulmonary, and renal disease was denied.

Physical examination revealed a well-developed, fairly well-nourished Negro man in moderate distress, experiencing dyspnea with paroxysms of cough. His pulse was 120 and regular; blood pressure, 110/60; respirations, 30 per minute, and temperature, 101.2 F. The skin was warm and showed no rashes, petechiae, or purpura. The pupils were round and equal and reacted to light and accommodation. The conjunctivae and sclerae were clear. The external auditory canals were clear and the tympanic membranes intact. There was partial mucous obstruction to the nasal pas-

Fig. 1.—Posteroanterior view of chest, showing bronchiolar and interstitial fibrosis, superimposed pneumonitis, and moderate hilar adenopathy.



Submitted for publication Aug. 18, 1958.

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sages. There was no pharyngeal injection or exudate. The neck veins were not distended, and there was no tenderness, masses, or rigidity of the neck. The thyroid was not enlarged, and the trachea was in the midline. There was absence of lymphadenopathy. The lung fields were noted to have decreased resonance to percussion, with fine moist rales throughout the upper two-thirds of the right lung field and the left base posteriorly. The heart was slightly enlarged to the left to percussion, and there was a regular sinus rhythm at a rate of 120 per minute. Pulmonic second sound was greater than aortic second sound, and no murmurs or rub were elicited. The abdomen

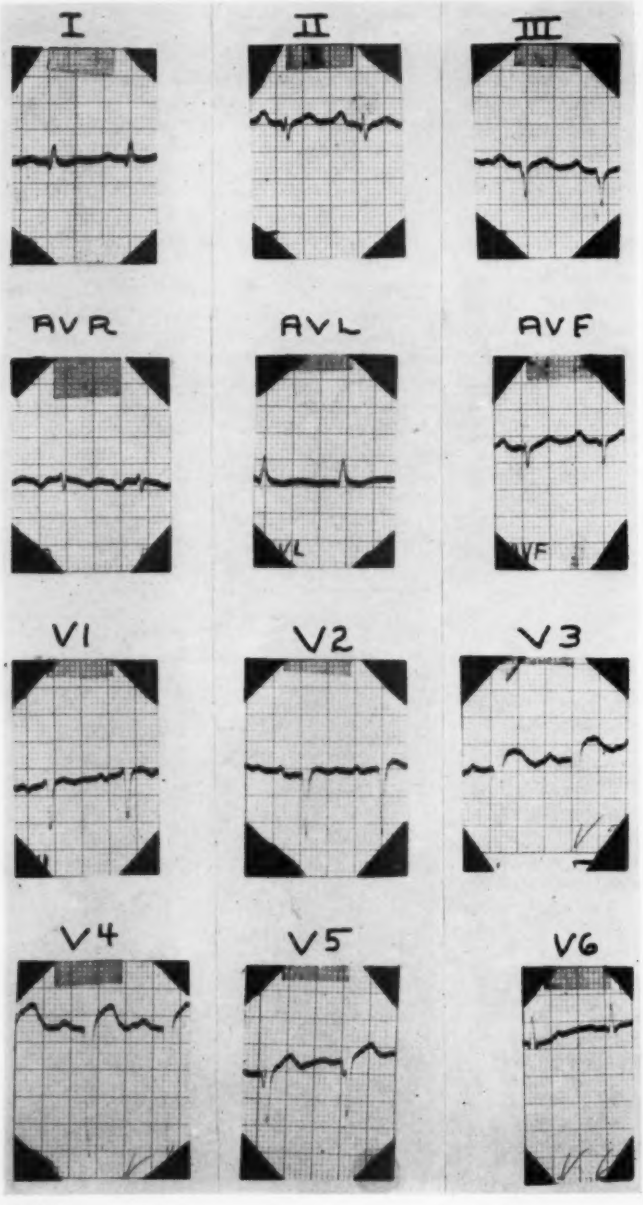

Chart 1.—ECG No 1; Sept. 12, 1955.

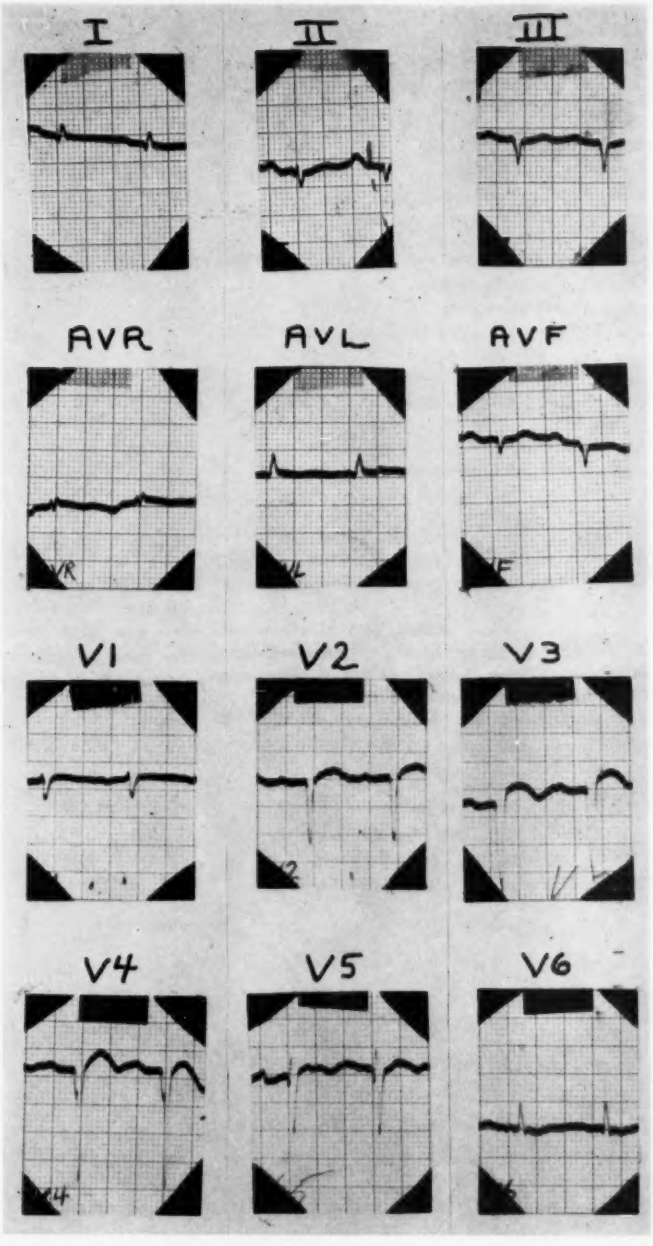

Chart 2.—ECG No. 2; Nov. 2, 1955.

revealed right upper quadrant tenderness to deep palpation. There was no rebound or masses. Liver, spleen, and kidneys were not palpable, and there was no ascites or costovertebral angle tenderness. There was no clubbing or edema of the extremities. Neurologic examination was within the limits of normal, and rectal examination was negative.

Admission laboratory data showed negative findings on urinalysis; hemoglobin, 15.5 gm.; white blood cell count, 6,300; sedimentation rate, 12 mm.

in one hour (normal 18 mm. in one hour); blood urea nitrogen, 11 mg. %; fasting blood sugar, 105 mg. %; serum cholesterol, 150 mg. %, and negative serologic tests for syphilis. The chest x-ray revealed a diffuse symmetrical interstitial and bronchiolar fibrosis throughout both lung fields, with reactive areas of pneumonitis involving the right upper lobe and superior segments of both lower lobes. The hilar shadows were moderately enlarged, and there was a slight increase in the transverse diameter of the heart (Fig. 1). An electrocardiogram taken shortly after admission revealed a sinus tachycardia, low voltage, and occasional premature ventricular contraction. The T-waves were low in Leads I and aV_1 and there was slight elevation of the ST segment, with biphasic T-waves in Leads V_2 through V_5. A Q-wave was present in Leads V_2, V_3, V_4, and V_5 (Chart 1).

Hospital Course.—A working diagnosis of extensive bilateral bronchopneumonia was made, and the following considered as part of the differential diagnosis: (1) pulmonary tuberculosis; (2) Boeck's sarcoid with superimposed pneumonitis; (3) fungus disease of the lung; (4) pulmonary adenomatosis, and (5) cardiac decompensation with pulmonary edema.

The patient was placed on penicillin, 600,000 units intramuscularly twice daily, and sulfisoxazole (Gantrisin), 1 gm. four times a day. The temperature continued to range between 100 and 101 F for the first ten days of therapy. He remained dyspneic and orthopneic, and continued to complain of epigastric distress. He would also vomit following the accumulation of a considerable amount of pharyngeal secretions.

Two weeks after hospitalization physical examination was essentially unchanged, except for an enlarging tender liver.

Additional laboratory data noted negative first- and second-strength PPD skin tests, as well as five negative sputum smears for acid-fast bacilli. A venous pressure was 140 mm. of water and circulation time (dehydrocholic acid [Decholin]) was 30 seconds. Four successive blood cultures revealed no growth. It was suggested that the patient might have an endocarditis with cardiac decompensation. He was digitalized, placed on a low-sodium diet, and given 2 cc. of meralluride (Mercuhydrin) intramuscularly twice weekly. Penicillin was discontinued and oxytetracycline (Terramycin), 2 gm. per day, was started. Again the next two week period was marked with temperatures ranging between 98 and 101 F, with no clinical improvement. Despite the apparent negative tuberculous work-up the patient was placed on streptomycin, 1 gm. daily for 5 days, followed by 1 gm. three times per week; aminosalicylic acid, 4.0 gm. three times a day; and isoniazid, 100 mg. three times a day. All other antibiotics were discontinued. However, during this second month of hospitalization there was no clinical or radiographic response. The cardiac regimen was likewise discontinued. Interval cardiogram (Chart 2) revealed serial changes compatible with an anteroseptal infarction. A scalene node biopsy was performed during the seventh hospital week and revealed a granulomatous inflammation consistent with sarcoidosis. Findings on a subsequent liver biopsy (Fig. 2) were also compatible with this diagnosis.

Interval laboratory data revealed a total protein of 6.0 gm. per 100 cc.; albumin 4.0 gm.; globulin 2.0 gm.; serum calcium 16.7 mg.; serum phosphorus 3.8 mg.; alkaline phosphatase 4.1 units; serum bilirubin 0.3 mg.; serum cholesterol 180 mg., and thymol turbidity 2 units. Heterophil agglutination,

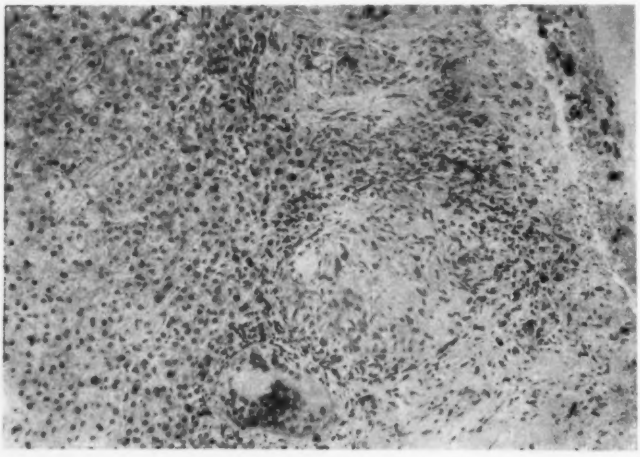

Fig. 2.—Liver biopsy specimen, showing epithelioid granuloma compatible with diagnosis of sarcoidosis.

lupus preparation, upper gastrointestinal series, intravenous pyelogram, and five sputum and three gastric cultures for acid-fast bacilli and fungi were negative or normal.

The patient was placed on cortisone therapy: 300 mg. the first day, 200 mg. the second day, and 100 mg. daily for a two-month period. The clinical response was immediate, manifested by a disappearance of fever, dyspnea, orthopnea, cough, and abdominal pain. The serum calcium returned to normal levels in two weeks, and the chest x-ray showed moderate clearing of the interstitial pneumonitis. The electrocardiogram after six weeks' steroid therapy failed to reveal the presence of

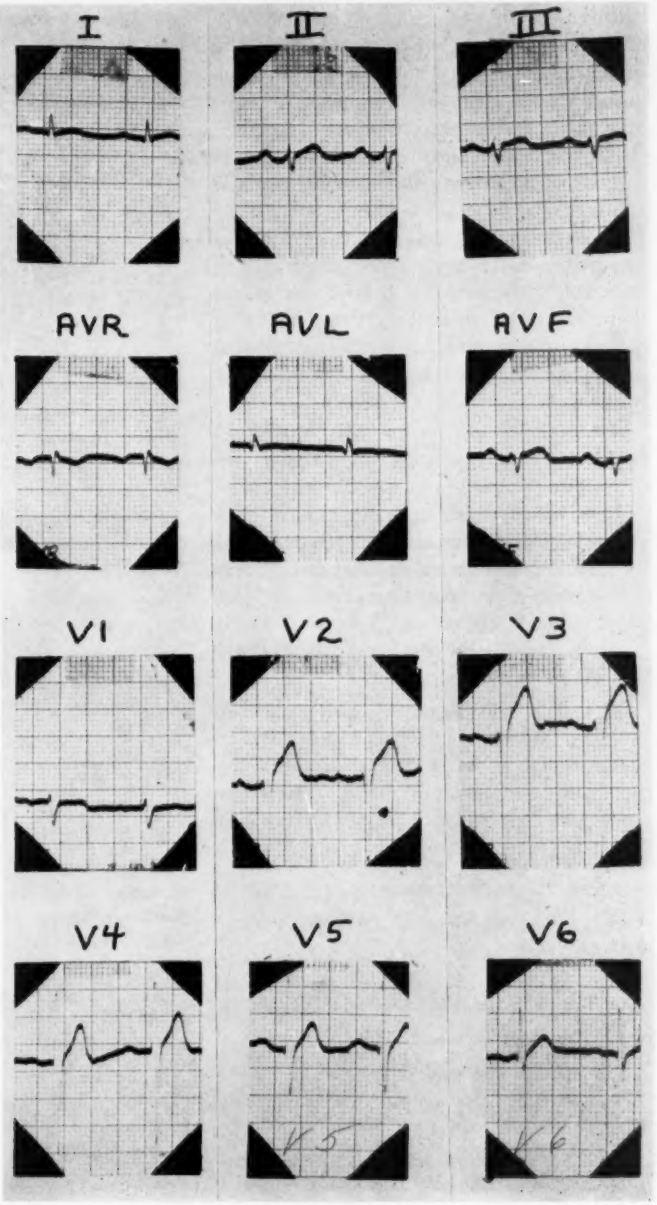

Chart 3.—ECG No. 3; Dec. 19, 1955.

the Q-waves in the precordial leads and was essentially within normal limits (Chart 3).

The patient was discharged to the chest clinic for follow-up after cortisone was discontinued.

Comment

Freiman has pointed out that direct involvement of the heart occurs in 20% of autopsied cases of sarcoidosis.[16] The myocardium may be massively infiltrated, including the coronary branches. Death may ensue due to heart failure.

Fatalities may also occur indirectly as a result of extensive pulmonary disease and subsequent right heart failure.[17]

Our patient's first electrocardiogram was interpreted as an acute anteroseptal infarction. After six weeks of bed rest, antibiotic therapy, and a cardiac regimen (including digitalis) there was no significant clinical improvement. The electrocardiogram was unchanged.

After biopsy evidence of sarcoidosis and cortisone therapy, a rapid improvement in the clinical status of the patient was noted.

It is felt that the coronary vessels or a portion of the myocardium was involved by sarcoid granulomata and that this process was reversed by cortisone therapy. The rapid disappearance of the Q-waves in Leads V_2 through V_5 on the electrocardiogram supports this hypothesis.

It is not the scope of this paper to evaluate the beneficial effect of steroids in the treatment of sarcoidosis. However, the metabolic (calcium) [18,19] and pulmonary improvement [20-23] parallels the observations of others.

Summary

Cardiac involvement in sarcoidosis is of considerable clinical importance.

For the first time Q-waves are reported in the electrocardiogram in a patient with acute fulminating sarcoidosis.

The electrocardiographic, as well as the other manifestations, of this disease entity were reversible with cortisone therapy.

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Reviews of Internal Medicine

Infectious Diseases

Annual Review of Significant Publications

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The first of these reviews, in 1935, dealt with 115 publications regarded as significant for citation. During the 1940's, the number exceeded 200, and in this issue there are 412. The progressive increase depended on several factors. For one, as in respect to insulin and diabetes, new remedies raised more problems than they solved. Others were the rise of virology owing to technical improvements in serologic, microscopic, and cultural procedures, the medical exigencies of two wars, increased financial aid from governmental sources and public money-raising campaigns for research, with the resultant increment of investigators and their publications. The resurgence of scientific endeavor in war-torn countries, especially Russia, added to literature subject to review. Interest in special fields shifted, as expected. Pneumococcal pneumonia, of importance before 1940, almost ceased to be a problem. Tuberculosis and the parasitoses, scarcely mentioned in early reviews, now are the objects of enough attention to justify separate treatment in these ARCHIVES, as in the case of syphilis.

As regards additions to knowledge in the past year, a number of new antimicrobics were judged, but no great advances were made. To the contrary, adverse criticism continued against indiscriminate therapy for the troubles it has raised, especially the specter of antimicrobic-resistant staphylococci. Numerous publications concerned Streptococcus and its bearing on rheumatic fever. The 1957 pandemic of influenza provided grist for the mills of many investigators. Much was learned about minor infections of the respiratory tract and about viruses previously confused with poliomyelitis.

Submitted for publication March 18, 1959.

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Antimicrobials

In 1956, about 1,300 tons of antimicrobials were made in the United States. They have saved thousands of lives, shortened many illnesses, and reduced the cost and time of medical care. Nevertheless, the hazards of their side-effects, though small in proportion, are increasingly serious. Penicillin, still the most useful agent, causes more disturbances than the others. About 10% of people are hypersensitive to it. Of 901 persons known to have had an allergic reaction, 83 died from anaphylactic shock. Tetracyclines gave rise to only three of such instances but caused many superinfections, especially enterocolitis. At least 15 cases of hemic dyscrasias were due to chloramphenicol.[1]

According to editorial comment, "There is clear and undisputed evidence that most infections arising in hospitals are caused by organisms resistant to the very antibiotics that are most widely used in the same institutions; yet the ardor of the medical profession for prescribing these antibiotics on every possible occasion, irrespective of any justification for their use or the existence of any proof of their value in the conditions for which they are prescribed, does not seem to have been dampened."[2]

Surgeons particularly continue to use penicillin and streptomycin routinely after all kinds of operations, in the blind belief that they are thus reducing the number and severity of postoperative complications. They may be disillusioned by the report of a controlled study.[3] In that study, penicillin and streptomycin failed to reduce the incidence of postoperative infections and those which did occur were caused mainly by antimicrobic-resistant staphylococci or Gram-negative enterobacteria. Antimicrobics used prophylactically failed in potentially contaminated cases as well as in "clean" ones. The infection rate was about the same, 5%, as it was 20 years ago. Apparently the kind of infecting bacteria changed without lessening the number of infections.[4] Nitrofurantoin given prophylactically after prostatectomy failed to reduce the incidence of fever or pyuria. Pseudomonas bacilli and staphylococci were not suppressed by therapy.[5] The mortality rate from severe burns increased from 19% to 69% between 1947 and 1956. The majority of deaths before 1947 were caused by shock; in later years infection was the chief factor. Antimicrobic therapy had no effect on the incidence of infection.[6]

Antimicrobics theoretically should suppress bacterial action in the intestine responsible for the production of ammonia, a factor in the cause of hepatic coma.[7] However, the relationship of ammonia to coma was inconsistent. Other toxic substances probably are involved. Of nine patients treated orally with neomycin or paromomycin, seven improved, but only three recovered.[8]

Chlortetracycline, oxytetracycline, bacitracin, and polymixin administered orally caused striking but inconsistent changes in the fecal flora. The tetracyclines caused a loss of body weight and an increased excretion of nitrogen and riboflavin in the urine. Studies failed to establish a relationship between these effects and the altered enteric bacteria. Bacitracin and polymixin caused a more striking reduction in bacterial flora but did not produce metabolic changes. The fecal excretion of vitamins did not vary in any consistent direction.[9]

Reasons for and against the use of combinations of antimicrobials were listed by Jawetz. None of the currently advertised combinations was more effective than one of the drugs in the mixture.[10] At last count, 69 preparations containing from two to five agents were on sale.[12] Penicillin with chloramphenicol served no useful purpose. Activity against a variety of bacteria was the same whether single doses of one agent or the two in the same total amount were used.[13]

Antimicrobics accumulate in large amounts in patients with oliguria; therefore, care must be taken to prevent toxic effects. During oliguria, maintenance doses of 250 mg. of streptomycin at two- or three-day intervals seemed adequate.[14] The "half-life" of penicillin G in two normal persons was 30 minutes, in contrast with 7 to 10 hours in oliguric patients; for tetracycline, the corresponding figures were 7 to 8 hours and 60 to 120 hours.[15]

Unexpected sequels were charged to the widespread use of antimicrobics. An increasing incidence of tubal pregnancy was thought to follow the treatment of salpingitis which preserved the tubal patency.[16] The apparent increased incidence of thyroiditis also was ascribed to the overuse of antimicrobics.[17]

Reactions to Penicillin.—Study of 30 fatal reactions showed that in 18 cases there had been little or no reason for therapy with penicillin. No inquiry had been made as to previous treatment in 14 patients; 3 patients had had asthma, and 10 had a previous reaction to penicillin. Lawsuits were instigated in nine cases. Physicians, therefore, should use great care because of their liability to prosecution. It is difficult to ascertain when a patient is or is not hypersensitive. Persons unknowingly may be sensitized by ingesting traces of penicillin contained in milk, by possible absorption of antigen from the skin on which penicillium may grow, and from other sources.[18] Penicillin in poliomyelitis and adenoviral

vaccines caused allergic reactions in six persons.[19] Penicillin "fall-out" in the pharmacy and in rooms where it is prepared for injection is another source of hypersensitization. Penicillin was detected in dust and in the nares of persons in those areas.[20]

To avoid reactions, it is of greatest importance to withhold the use of penicillin when no indication for its use exists. One physician "long ago abandoned the use of penicillin except where proper studies indicated it to be the only antibiotic capable of affecting a given organism . . ." and now uses broad-spectrum agents in his practice.[21] One wonders for what infections the broad-spectrum agents were used. Few diseases encountered in general practice demand antimicrobic therapy.

Erythrocytes can be sensitized to penicillin but not to other antimicrobials. Among 2,000 serums studied, 25 reacted specifically with "penicillinized" erythrocytes. Each of the 25 persons whose erythrocytes were sensitized had received penicillin in the past, but only a few had had clinical evidence of hypersensitivity. The significance of the antibody is under investigation.[22] Human serum also may contain specific antibody to penicillin. A test may be devised to determine the sensitivity of patients to penicillin in order to avoid serious reactions.[23]

Commercially prepared disks for the estimation of sensitivity of bacteria to antimicrobics may be faulty. In tests of 640 lots made by four manufacturers, there occasionally was a discrepancy between the statements on the label and the assayed potency. Some disks contained no antimicrobic, and the activity of others varied from one-tenth to three or four times the stated strength.[24]

New Antimicrobics.—There seems to be no end to new agents with complex names, carefully selected for the sake of euphony. It is hoped that discoveries will keep a step ahead of agents to which staphylococci successively become resistant. A few of the new ones are griseofulvin and malucidin, which are antifungal, framycetin, ristocetin, paromomycin, and kanamycin. Ristocetin is useful against staphylococci and enterococci sensitive to it and may be of value in treating enterococcic endocarditis. It must be given intravenously. Untoward effects are neutropenia, fever, rash, diarrhea, and thrombophlebitis in the vein used for injection.[25] It was used unsuccessfully in three patients with staphylococcal septicemia. The serum was bactericidal, but cocci persisted in the blood.[26] Ristocetin also kills mycobacteria. Resistance to it and cross resistance with other antimicrobics were said not to occur. Thrombocytopenia and other hematologic disorders occurred in eight patients, and two died.[27] Two patients with staphylococcal endocarditis were cured with ristocetin and erythromycin, but severe neutropenia and thrombophlebitis occurred in both.[28]

Kanamycin, discovered in Japan, is useful for the treatment of certain troublesome bacterial infections. It resembles neomycin and streptomycin and may cause similar renal and auditory side-effects. It is of value chiefly against bacteria resistant to other agents, particularly staphylococci and tubercle bacilli. Bacteria readily become resistant to kanamycin.[29] The agent and its effects were described in a monograph of 38 articles.[30]

Neomycin may cause fatal episodes of apnea, especially during anesthesia. Its neuromuscular toxic effect may be countered with neostigmine methylsulfate.[31] It also may cause deafness, and it is nephrotoxic. Yet neomycin had value in the treatment of infection caused by Proteus and Pseudomonas bacilli and staphylococci. It was said to be useful when given as an aerosol for bronchitis and pulmonary abscess.[32] Neomycin was injected intraperitoneally in 20 patients with peritonitis resistant to other antimicrobics. Seven died, but six of them from other cause.[33]

Polymixin B is nephrotoxic but is active in infections caused by Pseudomonas aeruginosa and staphylococci. It is effective

when applied topically. Bacitracin and tyrothricin have little therapeutic value.[32]

Tests failed to reveal any advantage of four new preparations of tetracycline introduced in the hope of attaining larger amounts of the agents in the blood than of the hydrochloride compound.[34] Dimethylchlortetracycline, derived from a mutant of Streptococcus aureofaciens, apparently is the most effective agent of the group, and a larger amount appears in the blood with comparable oral doses.[35]

Viral Infections of Respiratory Tract

Andrewes summarized knowledge of minor infections of the respiratory tract. Influenza A, B, and C, Sendai, and CA viruses are grouped as myxoviruses, distinct from adenoviruses and others. Influenza C virus seldom causes disease. Sendai virus found only in Asia is regarded wrongly as influenza D virus by some investigators. The significance of antibodies against it in persons in England and America is obscure. Most minor respiratory tract infections are of unknown origin. It is doubtful whether the newly discovered 2060 or JH virus and several others are important causes of the common cold. Probably a number of elusive viruses are implicated, each of which may change its nature from time to time, as influenza virus does.[36,37] Seventy newly recognized "respiratory" viruses were described since 1948,[38] and more are in the offing.[39]

During viral infections, changes in epithelial cells, called ciliocytophthoria consisted of nuclear degeneration, acidophilic cystoplasmic inclusions in intact cells, and fragments of ciliated tufts. These and a predominance of mononuclear cells in the exudate serve as early diagnostic aids to distinguish viral disease from bacterial infection with its polymorphonuclear cell exudate.[40]

The incidence of infections in families indicated that of numerous social and environmental factors only overcrowding and, with less certainty, inadequate clothing were conducive factors. Infection usually appeared to be introduced by children. Climatic changes increased both the introduction and frequency of colds into households. The number of infections was the same whether tonsils were present or absent.[41] Benign metencephalitis or acute inflammation of the pons and cerebellum was observed in two patients as a sequel to a minor infection.[42]

In families, minor infections of the respiratory tract accounted for two-thirds of all illnesses. As in other studies, the common cold predominated and the lower respiratory tract was involved in less than 1%. Less than 3% of illness was caused by bacteria, almost always group A hemolytic streptococci.[43] Obviously, antimicrobics were needed in less than 3% of patients. The symptomatic therapy recommended is the same as I outlined in 1946 (except that the pleasant effects of small doses of alcohol were not recited). In line with general opinion, prophylaxis against secondary bacterial infection is not warranted, except in special circumstances. As stated in 1946,[44] irradiation of air by ultraviolet rays, special diets or vitamins, tonsillectomy or adenoidectomy, antihistaminic drugs, and vaccines made from bacteria are worthless in prevention.

Respiratory tract infections in 122 adults were caused by influenza viruses in 10, Coxsackie viruses in 6, adenoviruses in 4, and mononucleosis in 2. Thus, viral infection could not be detected or identified in 75% of cases. Hemolytic streptococci accounted for 6%. Twenty-nine patients had fever, and, of these, influenza viruses accounted for 25%. Bacteria were found commonly in the rest but may have had only casual causal relationship.[45]

To gain a view of average pediatric practice in the antimicrobic era, Geppert reviewed facts about 10,000 children observed for a decade. By the age of 10 each child had had about 100 illnesses. Of these, 77% among outpatients were caused by viruses or bacteria, accounting for nine infections per child. Antimicrobics did not decrease the incidence but lowered the death rate to

less than 0.1%. Nevertheless, infections caused 20% of all deaths. Minor respiratory tract ailments caused 52% of all illness. Every child had had the common cold or pharyngitis, many six times a year; hence the need for pediatric "virologists and respiratoryologists" to care for 77% and 47% of patients, respectively, in office practice. The average child treated as an outpatient received nine therapeutic injections of penicillin during 10 years, but probably many without need. Tonsillectomy and adenoidectomy were deemed necessary in less than 4% of children.[46]

A study, made of 231 patients admitted to a hospital with disease of the respiratory tract, revealed 42% to be of viral origin, 12% of bacterial infection, 27% of combined infection, and the rest of undetermined cause. Of the bacteria involved, 17% were staphylococci, 16% pneumococci, 16% Pfeiffer bacilli, and 5% streptococci. The viruses of influenza A and B and one responsible for agglutinin to Streptococcus MG predominated. Cold agglutination rarely occurred.[47]

Influenza.—Space allows comment only on a few of the many papers about Asian A influenza in regard to its spread, clinical characteristics, serious complications, and problems of immunity and vaccination. The February, 1958, issue of *Public Health Reports* alone contained 13 articles. The pandemic was the first on which an organized attack was possible, but six months elapsed between the time the virus reached a research laboratory in the United States and the time influenza increased above the statistical epidemic threshold. Vaccine became available in large amounts two months after manufacturers received the virus.

The pandemic spread to every continent within six months after its recognition in China. According to Dunn, the dissemination was determined by seasonal changes,[48] but crowding and poverty also were factors. All reports agree as to the high morbidity, the low mortality as compared with the 1918 pandemic, and the fact that most deaths occurred in patients with other chronic diseases, especially of the cardiovascular-renal system and at the extremes of life.[49] The mortality rate slightly exceeded that of the A′ virus epidemic in 1953 but was lower than in the 1943 epidemic.[50] An estimated 20,000,000[49] to 80,000,000[51] people in the United States were sick. Claims for sickness against the National Insurance scheme in England totaled $28,000,000.[52]

The epidemic lasted eight weeks among 60 families of 308 people, in Cleveland. The virus was present in 87% of families and was isolated from 126 persons. In some households all members harbored the virus and, one-third to one-half of them were sick. The morbidity was highest in children. Of the 308 persons, the attack rate was 47%. The total serologic attack rate in unvaccinated children was 55%.[53] In an area of London, 930 cases were tabulated, an incidence of 17% of the physician's practice; 66% were in children and teen-agers. All illnesses were mild. Pneumonia and otitis occurred in 4%.[54] A second serious wave of the pandemic predicted later in the winter, as occurred in 1918-1919, did not follow.

Serious Consequences.—In a Scottish city, 125 patients entered hospitals; 69 had pneumonia, and 12 died; 42 had bronchitis, and 14 had laryngotracheitis. Seventy-three, 58%, had had chronic pulmonary disease. No significant bacteria were identified in 68, and in the rest staphylococci and pneumococci predominated. Antimicrobic therapy probably induced staphylococcal superinfections in 12, of which 4 were fulminating.[55] Similar circumstances were observed in Australia, where adults with pneumonia were treated with unnecessarily huge doses of 24,000,000 units of penicillin a day.[56]

In Denver, 23 fatal cases were studied post mortem. An unusual degree of laryngotracheobronchitis and a variety of pneumonias were observed. Pneumococci and staphylococci were present in 17. Almost all of the fatal cases included other chronic disease or debilitation.[57] In Chile also,

pneumonia in the presence of other disease or in infancy and old age was the chief cause of death. As in 1918, different bacteria predominated in different areas. Pneumococci were found oftenest in one community; staphylococci, Klebsiella, or Hemophilus influenzae, in others.[58]

Pulmonary lesions of Asian influenza resembled those of the pandemic of 1918. The virus was more pneumonotropic than the viruses prevalent between the pandemics but less so than the 1918 strain. Among 148 cases, influenza viral pneumonia, without bacterial invasion, was present in 20%. In 31% both virus and bacteria were operative, and in others bacteria alone were found. Staphylococcus pyogenes var. aureus was isolated from 59% of lungs; pneumococci, from 15%; colon bacilli, H. influenzae and hemolytic streptococci, from the rest.[59]

There still is obstinacy to accept the fact, recognized in 1918, that the virus of influenza alone gives rise to pneumonia. In an epidemic among military personnel in 1951, pneumonia occurred in 1% of cases and was called a "complication" instead of a feature of the severest form of influenza. Antimicrobic therapy, as would be expected, had no effect, and none died. Pneumonia appeared in one patient during therapy, and in another moniliasis resulted, probably from therapy.[60] The authors implied that influenza virus itself may cause pneumonia, as if it were a new idea. It is wise to be familiar with old literature.

Asian influenza affected 600 Boy Scouts at a jamboree, and a number had pneumonia that resisted antimicrobic therapy.[61] In this instance, the observers admitted that pneumonia may have been a part of the primary viral disease. Others inferred that influenza viral pneumonia now is possible because antimicrobics suppress bacterial invasion.[62] Patients with mitral stenosis are likely to have influenzal viral pneumonia,[63] and for these prophylaxis with vaccine is needed.

Extensive data were compiled in 30 patients with influenzal pneumonia. Of these, 24 had superimposed bacterial infection. Five of six with chronic cardiac disease and viral pneumonia died, and at necropsy the lungs were free of bacteria. In discussion of the essay, Levine suggested that death was caused by cardiac failure precipitated by infection. Sabin asked if there were evidence of encephalitis, such as he had seen in three patients, resembling von Economo's encephalitis associated with the 1918 pandemic. The replies were negative.[64]

Several patients with influenza were thought to have myocarditis or pericarditis, probably caused by the virus.[65] Others with gastrointestinal symptoms were suspected of having gastroenteritis, mesenteric adenitis, or appendicitis.[61]

Relation of Asian A Virus to Others.—Tests were made on samples of serum to detect antibodies against influenza viruses between September, 1957, and February, 1958, without information as to whether the donors of the blood had had influenza. According to the results, about 35% of the population was infected with Asian virus in October. A second abrupt increase occurred in January, but at that time serologic evidence of three different strains was detected. Two were similar to those prevalent between 1947 and 1956, and one was not.[66] Evidently, old strains may reemerge or change by combining or recombining with other genetic elements.

Antibody for Asian A virus was found in persons 60 or more years of age whose blood had been preserved before 1957 and tested afterward. Perhaps a virus like the Asian kind caused the 1890 pandemic and recycled as the Asian strain in 1957.[67,68] On the other hand, Asian A virus may be different and only share an antigen common to previously extant strains.[69] Furthermore, an antigen specific for a given virus does not necessarily indicate infection with that strain when it was prevalent, but it could have been evoked by infection with other strains at any time.[70] A question arises of whether the virus of the 1918 pandemic will ever reappear in its virulence. However,

outbreaks of B influenza already have appeared.[71a]

Among samples of serum collected from 285 persons from 1 to 95 years old, the antibody titer against Asian influenza was so low that the virus predictably will cause more epidemics in the near future. The amount of antibody against all three families of influenza B virus was great enough to forecast insignificant infections.[71]

In an epidemic of respiratory tract disease among students, viral pneumonia was present in 50. Antibody against Sendai virus increased in six. Of 110 patients with infectious mononucleosis, 13 also had the antibody, but Sendai virus was not isolated. It may have been causally related [72] or commensal, or the serologic reaction may have been unspecific.

Influenza Vaccine.—A monovalent Asian A vaccine reduced the incidence of febrile influenza by 90% in naval personnel.[73] Two other lots of similar monovalent vaccine and a polyvalent vaccine not containing the Asian strain failed to provide immunity.[74] All army personnel, in 1959, will be vaccinated against A, A^1, Asian, and B strains, contained in a single 1 cc. subcutaneous injection. Children 3 months to 5 years old may be given injections of 0.1 cc. intradermally twice.[75] Persons who received 200 CAA units of vaccine developed as much antibody as others did after having influenza. Reactions occurred in 18 of 619 volunteers.[76] With the use of a jet injection apparatus, over 700 injections of vaccine were given in an hour.[77] Unsolved problems of influenza were outlined by Mogabgab.[78]

Adenoviral Infections.—Adenoviral antibody was present in many people, but the viruses caused less than 3% of illness among civilians. Immunity probably was acquired from infections in childhood. By the age of 5 years, 80% of children have antibody against 1 or more of the 14 types of adenoviruses. In infants, maternal antibodies transferred placentally usually disappeared after six months. As a result of subsequent infections, antibodies against Types 1 and 2 virus often appeared before the age of 5 years and were then in the same proportion as in adults. Infections caused by Types 3, 5, and 7 virus were less common. The general use of vaccines against adenoviruses is not warranted for civilians.[79]

Undue ado is made about the few adenoviral infections in civilians as compared with military recruits. Why, for example, should college students or others of similar ages be more immune to infection? In certain years adenoviruses may be rampant and cause the majority of mild infections, as in the case of influenza. An epidemic due to Type 3 adenovirus affected 134 of 395 schoolboys with pharyngitis.[80]

Adenovirus Type 1 and staphylococci caused the "stuffy nose syndrome" of premature infants. Those who harbored either microbe alone were not affected. In another outbreak, a different virus plus staphylococci was the cause. The observations were said to favor the concept of viral-bacterial synergism.[81]

Pharyngoconjunctival fever may be caused by any of the adenoviruses. Three cases associated with Type 1 virus were observed.[82] During an epidemic among children in Sweden, adenovirus 3 was found in the stools of 23 of 25 patients and in 3 healthy persons and was present in sewage. Serologic studies confirmed its causal relationship. The symptoms were characteristic of pharyngoconjunctival fever, but in addition, half of the victims had nausea, vomiting, and diarrhea.[83] Obviously, viruses may cause disorder of the gastrointestinal tract or the respiratory tract or both. In that respect complexity arises, even though etiologic problems are clarified by the discovery of the cause. "Respiratory" adenoviruses may cause diarrhea, and enteric ECHO virus may cause colds.[84] New enteric cytopathogens, similar to known ECHO viruses, were discovered in the stools of children with colds. Serologic evidence indicated their activity in the patients.[89] Coxsackie virus caused viral pneumonia in pigs and sore throat in children.[85]

The observations are of interest with regard to the frequency with which symptoms of respiratory tract infection occur in viral dysentery. This should give no surprise, since herpes simplex virus also is heterotropic and causes disparate disease.

Antigenic variation, like that of influenza viruses, probably occurs among adenoviruses. Seven additional serotypes were isolated. Some, especially Type 7, had subtypes and comprise a group.[86] The complement-fixation test identifies the specific type of adenoviruses in agreement with the neutralization technique.[87]

Previous reports of intranuclear crystallization of adenoviruses were confirmed. Hexagonal crystals filled with clusters and rows of distinct and indistinct particles were Feulgen-positive, indicative of deoxyribosenucleic acid.[88]

Vaccination.—Adenoviral vaccine containing virus Types 3, 4, and 7 reduced the admission rate to a hospital for naval recruits with infection of the respiratory tract by 66%.[89] A reduction of 90% was reported in another military group. Vaccine is valuable to protect new recruits in the Armed Forces but, at present, is not recommended for civilians.[90] For children in schools and camps the matter may be of importance.[91] Vaccination probably would result in only 6% reduction of infections in children up to 10 years of age.[92] A table of indications for vaccination is available.[93]

The Common Cold.—Use of Virus 2060, isolated from patients with colds, apparently is widespread. A neutralizing antibody against it was found in persons in large cities. The virus was similar to JH virus and probably comprises one of a group of newly discovered agents.[94] Of 58 volunteers inoculated with JH virus, 11 were infected, regardless of the titer of antibody they possessed. Colds appeared in four volunteers—but also in two control subjects who were not inoculated. Attempts to isolate the virus from other persons with colds were not successful.[95] Andrewes did not ascribe much importance to these viruses.[36]

About 40% of 1,000 volunteers inoculated with cell-free nasal secretions from donors with a common cold got headache, sneezing, chilliness, and sore throat after 24 to 72 hours. Nasal discharge and obstruction, cough, and malaise followed. None had fever. Bacteria in the throat neither predisposed, prevented, nor complicated the induced infection.[96] With no evidence that bacteria play a part in colds, it is hard to justify Ritchie's idea of giving subminimal doses (90 mg. spread over three days) of tetracycline.[97,98]

The virus in nasal secretions was neutralized by mixture with immune globulin. Colds were caused in one-fifth as many volunteers inoculated with the mixture as in those who received unneutralized virus. The resistance of nasal epithelium to infection may not depend on circulating antibody.[99]

Myxoviruses.—Two new myxoviruses were isolated, Type 1 from children with colds and Type 2 from children with croup. They may represent agents of another segment of minor infections.[100] Type 2 virus caused cold-like illnesses six days after inoculation into the throat and conjunctiva of volunteers and gave rise to a specific antibody. Volunteers who got sick spread the infection to 18 other persons by contact.[101] Previous observations on the relation of CA (croup associated) virus to croup were confirmed by the isolation of a similar myxovirus from another patient.[102]

Viral Pneumonia.—In a 16-day period, 26 of 130 inmates of an institution had colds, 13 with pulmonary invasion. Cold agglutinin was present in seven, in low titers up to 1:16. In a fatal case, monocytes infiltrated the alveoli.[103]

In 16 patients with viral pneumonia not caused by influenzal or adenoviruses, the titer of cold agglutinin increased, and, surprisingly, in 13, the sedimentation rate of erythrocytes exceeded 90 mm. in one hour. The high speed was not due to erythrocytic clumping by cold and bore no consistent relationship to the cold agglutinin titer.[104] It may have been caused by an increased

amount of fibrinogen and globulins; yet these changes oftener accompany pneumococcal pneumonias. One wonders if the disease in the patients discussed was the so-called Fanconi-Hegglin pneumonic syndrome, wherein the globulins and sedimentation rate are increased and the Wassermann reaction is positive; yet the authors make no mention of it.

Fourteen children with viral pneumonia had cold agglutinin titer higher than 1:64. Filtered tracheal secretion from some of them caused pneumonia in inoculated volunteers. In two patients, pneumonia was "complicated" by erythema multiforme exudativum (Stevens-Johnson syndrome).[105] However, it is well known that a form of viral pneumonia is a characteristic part of the syndrome. Herpes simplex virus may be one of the causes of it or a commensal in it. As in several previous reports, the virus was isolated from a patient in whose serum the specific antibody titer rose.[106]

During a period of six years, about one in five patients with viral pneumonia had a cold agglutinin in their blood. The percentage of reactors varied from 14% to 38% in different years. The causative virus which evokes the reaction has not been discovered. In several patients, increases in both cold agglutinin and antihemagglutinin for influenza viruses suggested concomitant or sequential infection with influenza[107] or an anamnestic reaction.

In January, 1958, a large epidemic of acute respiratory disease arose in two English cities. Within a month, 104 children were admitted to a hospital, most of them with roentgen evidence of pneumonia. Antimicrobics had no influence on the infection. All victims recovered. Bacteria or influenzal viruses were not the cause. Virologic studies are under way.[108,109]

Adenovirus Type 1 was isolated from the lungs of a patient who died from viral pneumonia. Staphylococcus pyogenes var. albus also was present, probably as a commensal.[110] Coxsackie viral pneumonia in pigs apparently was the source of mild infections of children.[85]

Uncertainty persists about the cause of giant-cell pneumonia, but measles virus was present in the lungs of three debilitated children at necropsy.[111] Adenoviruses are not the cause of interstitial plasma-cell pneumonia.[112] Moser reported the isolation of a virus which may be related to the psittacosis group of agents.[113]

Cytomegalic-inclusion disease is well known in infants, but only 19 cases have been observed in adults, usually with other debilitating disease and in those who had been treated with antimicrobics or steroid hormones. Two patients had fibrotic interstitial pneumonia resembling the disease described by Hamman and suspected to be of viral origin. In neither were Pneumocystis carinii present. A latent virus or the exogenous invasion by one made possible by a reduction of resistance may be the cause.[114]

In Norway, positive serologic tests for ornithosis were demonstrated in 15 of 416 donors of blood. Among 820 patients diagnosed as having viral pneumonia, 11% had specific complement-fixing antibody.[115] Evidently ornithosis is prevalent in Norway and may represent the so-called fulmar disease.

Poliomyelitis

According to a statistical report, the incidence and mortality of poliomyelitis reached a record low in 1958. Half of the total number for 1957 and less than one-seventh of the annual average for the previous three years were tabulated. The reduction seemed too large to be attributed to the natural waxing and waning of epidemics and may be the result of vaccination.[116] On the other hand, the incidence of paralytic poliomyelitis in July, 1958, was greater than in the same period of 1957.[117]

The second report of an Expert Committee was published. Recommendation was made to register cases of paralytic poliomyelitis separately and to apply the term "aseptic meningitis" to nonparalytic infections, because other enteric viruses often cause similar disease.[118] The recommenda-

tion may be questioned. The term aseptic means free from living germs, and that is not the case; viral or nonbacterial are more appropriate adjectives, but etiologic terms are best. It would be of interest to learn how much of the reported decrease in the incidence of poliomyelitis was due to the recent recognition of sporadic or epidemic meningoencephalitic diseases caused by other viruses and to their exclusion from the statistics of poliomyelitis.

Tests on serums from 811 patients thought to have had nonparalytic poliomyelitis showed but little agreement with the diagnosis. About 10% of illnesses were caused by ECHO or Coxsackie viruses.[119] As had happened in Russia, Coxsackie virus Type 7 caused an infection diagnosed as paralytic poliomyelitis.[120] Coxsackie B5 virus and ECHO-2 virus also caused paralytic poliomyelitis, fatal in one instance. Evidently acute anterior poliomyelitis is a syndrome of diverse cause.[120a]

According to the Expert Committee report, vaccine had a considerable effect in reducing the incidence of paralysis in poliomyelitis. However, in several instances, vaccination did not seem to shorten the course of an epidemic and neither prevented infection nor restricted a dissemination of the virus. Great hopes were held for the value of live attenuated virus given orally for prevention.[118]

The hopes were both raised and lowered. Live attenuated poliovirus administered orally to inhabitants of the Belgian Congo apparently stopped epidemics of paralytic poliomyelitis in several localities.[121] Nevertheless, the value of the procedure was questioned, and possible untoward effects were cited.[122] Dick reviewed the matter critically[123] and found no evidence of superiority of attenuated virus given orally over formalized vaccine injected subcutaneously so far as durability of immunity is concerned.[124] In Clark's study, 14 children were vaccinated with inactivated virus and later given attenuated virus orally. Five children excreted virus with ominously enhanced neurotropic properties for monkeys, but it did not spread to other persons.[125] The power of poliovirus to paralyze is unstable and unpredictable and so theoretic expectations of safety are not firm enough to justify more than small controlled trials. Evidently, the matter is unsettled.

In children exposed to poliomyelitis, one or two injections of inactivated virus had no effect on fecal excretion of virus, as compared with unvaccinated children. The desirable opportunity of natural acquisition of active immunity therefore persisted. Vaccination did not seem to influence the incidence of infection in contrast with its reduction of paralytic disease.[126] On the other hand, in other studies virus was present less often and in smaller amount in the pharynx of vaccinated persons than of unvaccinated ones. Vaccination seemed to neutralize it. In regions of high standards of personal hygiene, poliomyelitis may be transmitted chiefly by air, and this may be a factor in maintaining the virus in the population.[127] According to these observations, immunity from vaccination may interfere with its natural spread.

About 65% of unvaccinated pregnant women had no antibodies against polioviruses, but two injections of vaccine reduced the incidence to 18%. Infants of these mothers had passively acquired antibody but lost about half of it in five postnatal weeks. After two injections of vaccine at age one year, antibody appeared, but in lower titer than that of the mothers.[128] Poliomyelitis occurred oftener in multiparous women than in primiparous ones. Between ages 25 and 29 the incidence was higher in women than in men, probably owing to the larger proportion of pregnant women, and was higher in pregnant than in single women. The incidence of paralytic poliomyelitis was increased in households where children had the disease.[129]

A sick parakeet was the source of a fatal attack of poliomyelitis. Virus was isolated from the bird and from its sick partner.[130] The observation suggests that hosts other than humans may carry the virus and brings to mind the earlier demonstration of polio-

myelitis antibody in chickens and domestic animals.[131]

Effort is underway to achieve specific therapy. Hyperimmune rabbit serum or serum obtained from vaccinated persons reduced the severity of poliomyelitis in monkeys as compared with untreated animals.[132] A simple rapid microtest was devised for demonstrating a precipitin reaction between minute amounts of poliovirus antigen and antisera.[133]

Viral Meningoencephalitis

According to Hammon, three groups of enteric viruses, namely, poliomyelitis, ECHO, and Coxsackie, may cause diseases which are clinically alike. Furthermore, the viruses share common antigens, and so the distinction between them is not clearcut, and it is becoming more difficult to establish them as separate entities.[134] In Connecticut, exact diagnosis was made in 33 of 56 cases of meningoencephalitis and of vague febrile illnesses. ECHO-9, Coxsackie A-9, and unclassified viruses were isolated oftenest, poliovirus only twice. Each of the viruses caused similar disease with a rubella-like rash.[135]

ECHO Viruses.—Epidemics of disease caused by ECHO virus-9, characterized by fever, headache, nuchal rigidity, pharyngitis, vomiting, and occasionally an exanthem or signs of neural involvement, were reported from Canada [136,137] and England [138] and were anticipated in Massachusetts.[139] An estimated 400,000 persons in Minnesota [140] and at least 28,000, or 4% of the population, in Milwaukee were infected. For every patient sent to a hospital, 200 stayed home with mild symptoms. All recovered, without paralysis. Virus was isolated from healthy persons in 24% of households.[141,142] Many inapparent infections, no doubt, occurred. In former years, patients with such symptoms were diagnosed as having nonparalytic poliomyelitis. In instances where a rash is present, rubeola, rubella, roseola, Boston exanthema,[137,139] and meningococcemia [143] may be suspected.

ECHO virus-2 was isolated from patients with meningoencephalitis during an epidemic caused by virus-6.[144] ECHO virus-10 differs from the others and probably belongs in another category.[145] There are now ECBO (bovine) and ECMO (monkey) viruses.

Coxsackie Virus.—In Kansas, a 12-week epidemic in the autumn of 1956 involved about 3,000 victims, an attack rate of 8%. Only 63 were sick enough to enter a hospital with pharyngitis, nuchal rigidity, and fever. The rest had headache, nausea, low fever, myalgia, and occasionally pharyngitis. Most of the victims were less than 20 years old. Coxsackie virus Group B Type 5 was present in 61% of stools, in 26% of throat washings, and in 11% of the spinal fluids tested. The virus when introduced into a family often affected all members. It was air-borne or conveyed by the fecal-oral route.[146]

Other Viruses.—While it was long suspected to be the case, a variety of wild birds was shown to be a potential source of the virus of Western equine encephalitis. The same, no doubt, is true for St. Louis encephalitis virus. Inoculated birds harbored virus for at least 10 months.[147] For the first time, an important agent of human infection was established in a cold-blooded vertebrate. Garter snakes were infected with the virus of Western equine encephalomyelitis.[148]

Several species of birds, especially crows and pheasants, are the main reservoirs of Eastern equine encephalitis. Man and the horse, probably infected by mosquitoes, are accidental victims. Most of the cases have occurred in Massachusetts, especially where swamps favor wild life. The incidence of infection in birds varied greatly from year to year, depending upon biologic factors conducive to epizootics. Corresponding outbreaks of the disease in man occurred 16 years apart, in 1938 and in 1955.[149]

As expected, the mortality rate of Japanese B encephalitis was 6.5%, much lower than previously reported. No doubt, it is actually even lower were it possible to add all mild and inapparent cases to statistics.

Neuropsychiatric sequels persisted nine years in 40% of survivors of an epidemic in Guam. Sequels after mumps encephalitis were fewer and milder.[150] Hammon described the same concurrent epidemics of mumps and Japanese B encephalitis. Apparently both viruses were introduced as new infections. Both disappeared from the population in the years afterward, probably because of the absence of factors essential to their survival.[151]

Of five patients with symptoms of meningoencephalitis in Ireland, four at first were thought to have poliomyelitis. Serologic evidence later suggested that a virus of the Russian spring-summer encephalitis-louping ill group was the cause.[152] Three epidemics of myalgic encephalomyelitis in Switzerland were similar to those reported from other parts of the world. It has been called epidemic neuromyasthenia and was also mistaken for nonparalytic poliomyelitis. There were no changes in the spinal fluid; all patients recovered without sequels, and virologic studies failed to reveal the cause.[153]

West Nile fever involved 419 patients in Israel in 1957. Meningoencephalitis occurred in only 25% of senile patients and rarely in younger ones. Fever, lymphadenopathy, and an exanthem occurred, and intestinal or respiratory tract symptoms occasionally were noted.[154]

Mumps

Among 30 cases of mumps meningoencephalitis in children, 13 had no parotitis at any time; 12 had parotitis prior to and 2 concomitant with and three after the neural involvement. Complications or sequels were absent, except for one convulsive disorder two years later.[155] Purpuric thrombocytopenia followed two weeks after the onset of mumps in three adults.[156] Cortisone and corticotropin seemed to cause rapid remission of headache of meningoencephalitis. Orchitis and additional salivary gland involvement appeared in one patient during treatment. Prompt recurrence followed abrupt cessation of therapy. The duration of disease was not shortened in any of five patients.[157]

Two patients had viremia early in the disease when no antibody was present.[158] According to editorial comment, there are no satisfactory means to prevent mumps. Hyperimmune γ-globulin may provide weak passive immunity. Active immunity induced by vaccine cannot be evoked soon enough after exposure to infection to be useful, and when it does appear it is brief.[159]

Measles (Rubeola)

Seven patients who died of measles were studied at necropsy. Three in the early stage had characteristic generalized infiltration of giant cells in lymphoid tissue and secondary bacterial invasion. Koplik's spots seemed to be the result of trauma in areas of abnormal buccal mucosa.[160] Another had Alagna, Finkeldey, or Warthin cells, inclusion bodies in the bronchial epithelium, and cytoplasmic granularity in the macrophages of the lymph nodes and spleen.[161] Three children with chronic debilitating disease but no clinical evidence of measles had "giant-cell pneumonia," and measles virus was present in the lungs. The virus probably was the cause. Illness characteristic of measles occurs in children previously healthy.[111]

Gamma-globulin, given to one child five days after exposure and to another one day after the exanthem appeared, failed to prevent encephalitis.[162]

Measles virus, passed 24 times in the brains of suckling mice, when inoculated into other mice caused death in most of them 7 to 13 days afterward.[163] An attenuated virus used as a vaccine caused no lesions in mice but evoked high titers of immune bodies. Trial of vaccination of susceptible children is planned.[164]

Measles and canine distemper probably are related. They have in common a similar incubation period, similar localization and exanthem, demyelinating encephalitis, and characteristic giant cells.[165]

German Measles (Rubella)

Arthritis, seldom a sequel of rubella, was observed in 10 women. The latex-fixation test, believed to be specific for rheumatoid arthritis, gave a positive reaction in nine but a negative one in five of seven rubella patients without arthritis. The test probably is a nonspecific one or an indication of a rheumatoid trait.[166]

Various mixtures of virus, γ-globulin, and convalescent plasma were tested for their immunizing effects. Only virus with convalescent-phase globulin protected all six children in the several experimental groups. Passive protection was thought to be achieved by early administration of large doses of γ-globulin. At present, nothing has exceeded active immunity after the disease itself is induced in young girls to prevent rubella and its serious effects on the fetus during later pregnancy.[167]

Vaccinia

Vaccination of a patient with antismallpox vaccine to prevent recurrent herpes simplex incited superinfection of an active herpetic lesion by vaccinia virus. Both viruses obviously caused concurrent infection, and one did not interfere with the other. Since evidence of cross immunity is unproved, there is no justification to immunize patients with vaccinia to prevent herpes. In another patient, a large ulcerative lesion of the lip and cheek was caused by contact with a vaccinated sibling.[168] Seventeen days after vaccination, a man had pericarditis thought to be allergic in nature.[169] It may have been caused by the virus itself.

Two kinds of inclusions were found in vaccinia: an A-type of homogenous blue-staining substance or the Guarnieri body in sections stained with hematoxylin and eosin and a B-body of deep red material. The so-called Guarnieri body in preparations stained by Giemsa's method was the B-type.[170] Virus particles can be counted accurately by use of a new technique.[171]

Orf, said to be an infectious disease distinct from vaccinia, is contracted from sheep. The disease was prevalent among lambs in Ireland, and four cases in humans were observed.[172]

Neonatal varicella was fatal in 20% of cases. Necropsy made on an infant showed lesions in most organs.[173]

Viral Hepatitis

At least 8% of 2,000 persons in a college got hepatitis during an epidemic of undetected origin. The infection was distributed uniformly, but the incidence was higher in dining room servants. There were no secondary cases in the families of persons involved. The incidence of the disease in persons who had had hepatitis previously was the same as in those who had not. Gamma-globulin was used prophylactically after the epidemic declined and may have prevented a second epidemic wave.[174]

Outbreaks of hepatitis in closed institutions are not always transmitted by the fecal-oral route. Study in a prison incriminated needles used to inject narcotics illicitly. Because of the prevalence of hepatitis in jails, it is not wise to use prisoners as donors of blood.[175]

About 1,000 soldiers who had had epidemic viral hepatitis answered questionnaires regarding their health after six years. The recurrence rate was 8.3%. In only 3.2% did ill health persist. None had subacute necrosis or later cirrhosis.[176] Inapparent or mild, nonicteric, easily overlooked viral hepatitis, in some cases, may lead to otherwise unexplained cirrhosis. The event was observed in eight middle-aged or elderly women[177] and is reminiscent of the fatal cases in women reported from Denmark about 15 years ago.

The value of γ-globulin for immunization is undetermined. Follow-up studies over five years of nearly 11,000 persons who had been injected with γ-globulin and of the same number who had not failed to reveal a significant degree of protection.[178] Gamma-globulin was used to control an epidemic about a fortnight after the outbreak began. Fifty boys were treated, but nine got hepatitis and six had abortive disease.[179]

Endemic viral hepatitis affected about 350 persons in an institution in a five-year period. Gamma-globulin for prophylaxis reduced the incidence of disease from 20 per 1,000 in untreated subjects to 7.4 per 1,000. When the dose was increased, the respective figures were 22.5 and 1.7 per 1,000. Protection seemed to endure for seven to nine months. In addition to the injection of γ-globulin, live virus was fed to 16 persons to induce passive-active immunity, despite the danger of causing infection, but the results were inconclusive. During eight weeks, virus was present in the stools of persons who ingested the fecal filtrates.[180]

Hemagglutinin for chicken erythrocytes was demonstrated in the serum of the majority of cases of hepatitis. The reaction may serve as a diagnostic aid to differentiate hepatitis from jaundice due to other cause.[181] Liquid plasma stored at room temperature for six or more months did not cause hepatitis in any of 282 patients. Evidently the virus, if present, succumbs during storage, and plasma is safe for use.[182]

Viral Dysentery

One or more viruses account for the majority of epidemics of mild diarrhea in the United States. Fifteen years ago, during a large epidemic, I transmitted a mild diarrheal disease to volunteers by means of filtered bacteria-free feces from patients.[183] The experiments were confirmed and extended by Gordon and others. Yet, the usual reluctance to accept a new idea followed until many enteric viruses were discovered 10 years later. My suggestion of an appropriate term, viral dysentery (bowel trouble caused by a virus), also is resisted, although it fits nosologically with bacterial and protozoal dysentery.

More than 46 enteroviruses have come to light, but it often is impossible to prove their causal or their commensal relation to enteric disease. Yet serologic evidence of the pathogenicity of ECHO Virus 18 was discovered in infants with diarrhea.[184] ECHO, Coxsackie, polio, and adenoviruses were associated with "summer" diarrhea in 44% and enteric bacteria in 22% of 153 children. Infection with both bacteria and viruses was operative in 15%.[185] I had previously described a dual epidemic caused by an unidentified virus and Shigella. It may be, as in the case of respiratory tract disease, that minor enteric viral infections predispose victims to secondary bacterial invasion.[187] Anyway, nondescript summer diarrhea in children may be caused by a variety of enteropathogenic viruses and bacilli.[188]

Sommerville isolated 75 ECHO, Coxsackie, poliomyelitis, and unclassified viruses from 22% of 338 children with diarrhea, oftenest ECHO-7, Coxsackie A-9, and polio Type 1, but their causal relation was not supported by serologic evidence. From a control group of 115 children with respiratory tract disease, 17 enteroviruses were isolated. A combination of Shigella sonnei and ECHO or Coxsackie viruses was present in 23 instances.[186]

Over a period of a week, 33% of 1,256 persons in a Japanese hospital suffered from an acute, mild, diarrheal disorder supposedly caused by tainted food. The incubation period was 3 to 10 days. The onset was sudden, and 67% had fever with leukopenia, usually lasting two to three days. Oral administration of an undescribed inoculum, presumably of suspected food, caused symptoms in volunteers after three days but not in convalescent patients. Oral ingestion of fecal filtrates failed to do so. It was regarded as a newly recognized form of viral dysentery.[188] The possibility of the presence of a toxin was not ruled out.

Coxsackie Viruses

A number of children with sore throat probably contracted the infection from pigs with viral pneumonia caused by a Group A Type 5 virus.[85] A rise of the titer of neutralizing antibody and the isolation of Coxsackie viruses Group A Type 1, and Group B Type 3 indicated these agents to be the cause of acute benign pericarditis in two adults.[189] Coxsackie virus caused myocarditis, meningoencephalitis, and hepatic

and adrenal necrosis in newborn infants. In most instances the mother had had a febrile illness shortly before.[189,191] Meningoencephalitis was discussed on a previous page.

An unusual outbreak of primary interstitial myocarditis in Israel affected 57 infants and children, of whom 50 died. At necropsy lymphocyte-like cells infiltrated the myocardium. The cause was not found.[192] Possibly Coxsackie virus was implicated?

Herpes Simplex

Since fever often activates herpes simplex, test was made to see if temperature influences the growth of the virus in tissue culture. Virus failed to grow between 20 C to 28 C; some growth occurred at 30 C and at 40 C, with the greatest at 35 C. Virus survived best at room temperature, less well at 35 C, and not at 40 C. Evidently fever temperature alone did not favor the growth of the virus.[193] On the other hand, herpes simplex often erupted in patients treated by hyperthermia when the procedure was in vogue. Optimal growth in vitro may differ from growth in vivo. The virus of herpes simplex was present in fetuses of rabbits infected with the virus, evidently by transplacental passage.[194]

Herpes zoster without dermal lesions is difficult to diagnose; yet such instances occurred with muscular pareses, dermal pain, visceral, labyrinthine and geniculate involvement, and ophthalmitis.[195]

Salivary Gland Virus

About 18% of children less than 4 years old in Washington and 60% to 80% elsewhere had serologic evidence of infection with the salivary gland virus. A high percentage of children had the virus in their saliva and urine, without evidence of disease.[196]

There is uncertainty as to what causes cytomegalic inclusion disease. Routine examination of the salivary glands in premature infants and in children up to age 14 revealed inclusion bodies in 10%. Generalized infection occurred in 1%. Diagnosis rested on the demonstration of giant cells, with inclusion bodies in tissues, urine, or saliva.[197] The infection, uncommon in adults, is found chiefly in debilitated persons. In three adults with lymphomas it was a terminal event.[198]

Mononucleosis

A number of cases reported to be infectious mononucleosis with unusual manifestations probably were of other origin. Both an increase in the number of monocytes and a heterophile reaction in titer of at least 1:56 in unabsorbed serum should be present.[199] Studies of 100 cases, with criteria of definitive and presumptive diagnoses, were published. Diagnosis depends upon both clinical and laboratory data. Prednisone gave symptomatic relief but did not shorten the duration of disease.[200]

Other Studies

A missing link in the epidemiology of Colorado tick fever was supplied by the discovery of the virus in wild rodents, probably the reservoirs of infection. The virus had been demonstrated previously in man and in the wood tick.[201] An agent related to the psittacosis-lymphogranuloma group was isolated from a patient with trachoma. A blind volunteer was infected experimentally with the virus.[202]

In serologic studies on residents of the Amazon Valley, neutralization tests gave positive results for yellow fever in 45%, Ilheus virus in 36%, Venezuelan equine encephalitis in 17%, and Semliki Forest virus in 14%.[203]

No antiviral therapeutic agent has been discovered, but research is concerned with substituted benzimidazole ribosides, dicarbonyls, and thiosemicarbazones. So far, their activity was not striking, except against the virus of Rift Valley fever. It is optimistic to expect any one agent to attack all viruses.[204] Extracts of a seaweed inhibited the growth of influenza B and mumps virus and gave significant protection to mice infected with influenza.[205]

The virologic diagnostic laboratory has become an essential part of a hospital. Improvements and simplification of methods make it possible to diagnose many viral infections encountered in general practice.[206] A new chromatographic technique and purification of viruses and rickettsiae by cellulose anion exchange columns serve to remove extraneous material as demonstrated by electron micrography. The procedure may aid in further research.[207] A bacteriophage, the size of small viruses, passed through the intact gastrointestinal tract and skin of mice, as in the case of Pasteurella tularensis and Brucella melitensis. Perhaps some viruses may invade the body by the same routes.[208]

"New" Viral Infections

Infectious diseases portrayed as new ones seldom, if ever, are really new. Ones like coxsackiosis may be sorted out and newly recognized; others, absent for years, may crop up to be recognized, as in the case of influenza in 1890 and 1918, or a virus may invade a virgin community, as happened when explorers brought measles to the Pacific islands. Theoretically, new pathogens may originate by genetic recombination of viruses and cause genuinely new diseases.

Viral Infection (?) of Urinary Tract.—Acute nonstreptococcal nephritis was suspected to be of viral origin.[209] A patient with Coxsackie disease had viremia, viraliquoria (virus in spinal fluid), and viruria. Evidence of renal disturbance was indicated by the retention of injected phenolsulfonphthalein.[210] There is no reason why viruses cannot attack the kidneys. They have been recovered from the urine in rabies, lymphocytic choriomeningitis, and salivary gland disease, and numerous viruses in simian kidneys have confused investigators dealing with tissue cultures. Histologic renal lesions occur in poliomyelitis, influenza, mumps, varicella, rubeola, viral hepatitis, and yellow fever. Perhaps abacterial pyuria or viral nephritis occurs, as do viral pneumonia, viral hepatitis, and viral dysentery, but, so far, interest in the idea lags.

A filtrable agent, similar to the Russian spring-summer viruses, caused Kyasanur Forest disease in India. It affected chiefly the hematopoietic and visceral organs but not the brain. Two infections occurred in laboratory workers during research on the problem.[211] An unidentified infection caused an epidemic and 300 deaths in Thailand. It may be the same as Phillipine hemorrhagic fever.[212]

Ardmore disease, observed in Oklahoma in the autumn of 1955, was characterized by infection of the upper respiratory tract, severe prolonged malaise, general lymphadenopathy, hepatosplenomegaly, and a course lasting several months. Hepatic biopsy revealed mild inflammation. The cause was undiscovered, but a virus was suspected. The disease may be confused with infectious mononucleosis and may have been the one described by others as anicteric hepatitis.[213]

Goto described a disease in Japan called kyushoka. Sausage was incriminated as the source of infection. Volunteers, after ingesting sausage or after inoculation with the blood of victims, had symptoms four to nine days later, consisting of headache, malaise, pain in the back, chills, arthralgia, diarrhea, and leukopenia. The cause was thought to be a virus.[214]

Tuberculosis

According to a report of the National Tuberculosis Association, 55,000,000 persons in the United States have been infected with Mycobacterium tuberculosis and probably 3,000,000 eventually will have active disease. About 80,000 new cases are reported annually. The death rate now is the lowest ever—8 per 100,000 persons.[215] Deaths from tuberculosis in Great Britain diminished from 23,551, in 1947, to 5,573, in 1956.[216]

Treatment of 500 tuberculous patients with modern methods showed 92% of satisfactory results and a reduction of 50% in the cost of hospital care, as compared with previous experience. However, the

number of new cases and the extent of disease in these patients has not declined. Drug therapy must be accompanied by attention to individual needs of the patient and, when indicated, by surgical procedures. Practical instructions were outlined. Of interest is a statement that, of the drugs used, para-aminosalicylic acid is the most expensive, the least effective, and the most toxic. Streptomycin may cause nephritis, especially in renal tuberculosis.[217] Despite adequate medical therapy, closure of cavities was achieved in only 50% of patients after 12 months. Surgical procedures were done in the rest. Cycloserine is less effective than the commonly used antimicrobics but may have value when the urgency of the problem outweighs the risk of its toxicity. Pyrazinamide with isoniazid is no more effective than other combinations, and it is hepatotoxic. Streptovaricin as a single agent is not of much value.[218]

In the report of a conference on chemotherapy, the effects of new agents, such as cycloserine, pyrazinamide, streptovaricin, thiocarbanidin, and kanamycin, were evaluated.[219] Streptovaricin, given to guinea pigs infected with tubercle bacilli resistant to streptomycin and aminosalicylic acid, caused regression and healing of lesions that had been progressive when treatment began. All control animals had extensive tuberculosis.[220] The problem of drug resistance in tuberculosis is unsolved but probably is less serious a menace than was feared. About 1 in every 20 patients previously untreated with antimicrobics was infected with drug-resistant strains.[216]

A 14-year follow-up study of 80 patients who had had pulmonary resection for tuberculosis showed 85% to be well and free of tubercle bacilli. Factors favorable to good results were unilateral disease, a stable lesion, bacillus-free sputum before operation, preoperative antimicrobic therapy for 30 days or more, total antimicrobic therapy for 180 days, and, if present before, prompt disappearance of tubercle bacilli after operation. Most patients with poor results had bacilli in their sputum at the time of resection.[221]

Struthers led a program to control tuberculosis in a region of high incidence in Korea. Far-advanced disease was found in 34% of 1,000 patients. The organization of free clinics, beds in hospital, visiting nurses, and treatment with isoniazid and aminosalicyclic acid resulted in eliminating tubercle bacilli from 67% of 162 patients. Eighty per cent showed radiographic improvement after a year.[222]

Nine children received intramuscular injections of penicillin from a syringe apparently contaminated with tubercle bacilli. Abscesses developed locally with regional lymphadenopathy, in one child with miliary dissemination. Healing in most victims occurred after four to six weeks of therapy with isoniazid and streptomycin, but complete recovery required several months. One child had been vaccinated with BCG, and in him the appearance of symptoms of the primary focus were delayed for three months. The lesion was excised, and the lymph nodes were not involved.[223] In a community where histoplasmosis is rare, calcified pulmonary shadows in the lung were assumed to be tuberculous in origin. In plotting the shadows on roentgenograms of children, primary tuberculosis had no special areas of selection.[224]

Nontuberculous pneumonias observed in 36 of 695 patients with pulmonary tuberculosis usually were clinically atypical. In instances where etiologic diagnoses were made, 10 were caused by pneumococci. In 18, a mixture of Neisseria catarrhalis, α-streptococci, and staphylococci was present in the sputum. A virus may have caused some of the lesions. Tuberculosis was not activated, and no deaths occurred.[225] Were some of the pneumonias tuberculous in origin?

A committee recommended the cessation of mass roentgenography to discover victims of tuberculosis because of the great decline of the infection in certain regions. Search should be restricted to persons exposed to

infection in institutions and to low-income and migrant workers. For mass studies, the tuberculin skin test should be applied first and roentgenograms made of those who react to it. The procedure will be worthless if BCG vaccine is used.[226] Because tuberculin-positive persons are more apt to contract tuberculosis than nonreactors, the sensitivity excited by BCG vaccine in nonreactors will be confusing. Now that many adults are nonreactors, the tuberculin test should be applied in any case for the diagnosis of pulmonary disease of doubtful cause.[227]

BCG Vaccination.—Question often is raised about the possible reversion to virulence of strains of BCG and the homogeneity and stability of vaccine. Aside from a degree of heterogenicity, study of the matter revealed no proof of qualitative or of profound dissociative changes of BCG since its origin. A system of control and methods to ascertain its safety, identity, and antigenicity were outlined.[228] BCG vaccine given orally to a number of nurslings apparently caused tuberculous otitis.[229]

Dr. Aronson, who died in October, called attention to the disproportionate enthusiasm for BCG vaccination, as compared with that for poliomyelitis, in England where, in 1954, there were 8,000 deaths from tuberculosis and 700 deaths from poliomyelitis. He summarized his 20-year experience with BCG vaccine. Among vaccinated Amerinds, tuberculosis caused 12% of all deaths, but, among control persons, tuberculosis caused 45% of deaths. He agreed with general opinion that mass vaccination in areas of low incidence of tuberculosis is unnecessary, but persons exposed to the disease should be protected.[230]

Despite the reported favorable result, criticism of vaccination persists. Trials in Puerto Rico and the southeastern United States gave much less striking effects. Because BCG cannot protect persons who are already infected and may be helpful to only a small portion of those who may become infected in the United States, the disadvantages of vaccination outweigh its advantages. The risk of developing tuberculosis was much greater in persons who reacted to tuberculin than in those who did not.[231,232]

The belief once held by many that hypersensitivity to tuberculoprotein is an asset is contradicted by evidence that it is a liability, as maintained by J. A. Myers for 25 years. Granting this, how can the hazard be reconciled with the advice of national authorities and committees to vaccinate persons who are tuberculin-negative to induce tuberculin hypersensitivity? And with Aronson's views? Evidently, allergy alone does not confer immunity, but perhaps resistance to infection depends on a fine balance between degrees of natural resistance, acquired immunity, and allergy. It is disappointing that a problem studied for so many years still is so far from solution.

Inhalation of BCG bacilli by guinea pigs evoked tuberculin allergy, immunity, and resistance to subsequent air-borne infection with virulent tubercle bacilli. Allergy and immunity depended on the multiplication of BCG bacilli (infection!) in the animals. Treatment with isoniazid prevented the development of immunity.[233]

Prophylaxis with Isoniazid.—The question arises as to whether chemoprophylaxis with isoniazid excels vaccination with BCG. Isoniazid did not merely postpone or suppress the appearance of serious tuberculous complications but actually prevented them. Among 2,750 children treated with isoniazid, extrapulmonary extension occurred in only 5, as compared with 26 who were given a placebo. Adverse pulmonary changes occurred in 21 and 34 children, respectively, but the figures are not significant statistically.[234] Favorable results were reported by others.[235] Prophylaxis with isoniazid has one advantage over BCG: it does not interfere with the tuberculin reaction and its diagnostic value.

Other Studies.—Hyperthyroidism induced in rabbits increased resistance to infection with tubercle bacilli, suppressed already existing tuberculosis, and diminished the number of bacilli in the lungs. Induced

hypothyroidism, like the effect of cortisone, reduced resistance and increased the number of bacilli in the lesions.[236]

Culture of suspected tuberculous material on artificial media was more reliable than the inoculation of guinea pigs for the isolation of tubercle bacilli.[237] Chromogenic, acid-fast bacilli caused scrofula in children. The tuberculin test gave a positive reaction, and pulmonary lesions were absent.[238]

Soltys discussed the public health aspects of tuberculosis in domestic animals and birds in relation to man. Dogs and cats, though rarely infected, are a great risk in the dissemination of tuberculosis in a family.[239]

Leprosy.—Rogers reviewed 50 years of literature on the control of leprosy. Purposeful survey in India brought to light eight times as many cases as reported in the official census. The incidence is greatest in Nigeria and East Africa. Only patients with mucocutaneous leprosy[56] need strict isolation, and this form comprised about one-fifth of cases. The old method of isolation is unsatisfactory and leads to concealment of the disease. The establishment of villages for lepers, from which uninfected persons are excluded, is more effective. The greatest therapeutic advance in the history of the disease was the application of sulfones. Yet, in many treated patients, bacilli persisted in nodules. In one series of 800 treated patients only 11% had been freed of bacilli.[240]

Typhoid

Thirty-four cases of typhoid, one of them fatal, arose from polluted water imbibed at a summer religious meeting in Missouri. The epidemic resembled one caused by amebas during the World Fair in Chicago in 1933; typhoid did not ensue, and diagnoses were not made until two or three weeks after the victims had returned to their eight widely scattered resident States. Bacilli of Type C-2 probably were introduced into well water by a known carrier and caused 17 of the cases in which study was made; Types N, C-1, and W each caused 1 case. Of interest also was a preceding outbreak of mild diarrheal disease affecting 56% of the 500 participants within a few days of arrival at the camp.[241] The circumstances strongly suggest viral dysentery. This mild illness may have favored infection with typhoid bacilli which otherwise might not have occurred. I observed a case in point concerning bacillary dysentery, as mentioned previously.[187]

Vulvitis and vaginitis were unusual localizations during typhoid. Genital lesions were not uncommon 50 years ago.[242]

Salmonellosis

Enterobacteria, particularly Salmonella, circulating in the blood may find a nidus in atherosclerotic arteries and cause infection with perforation. The event may happen oftener with the increasing incidence of longevity, atherosclerosis, and salmonellosis.[243] Salmonella causes infections of widely different nature, including abscesses, meningitis, pleurisy, pneumonia, endocarditis, pelvic and urinary tract infection, prostatitis,[244] septicemia, toxemia, and typhoidal disease.

Strains of Salmonella typhimurium tested prior to 1948 all were sensitive to tetracycline. Of cultures of the same types of strains studied after 1956, nine per cent of those isolated from fowl and five per cent of those from man were resistant. Resistance presumably developed after the addition of tetracyclines to poultry food.[245]

Shigellosis

Three studies in Israel indicated the increasing resistance of Shigella to antimicrobics. About 50% of strains resisted sulfadiazine,[246,247] and 20% to 35% resisted tetracycline and chloramphenicol, whereas all were sensitive in 1954.[248] Similar results, including streptomycin, were noted in Hungary.[249] All strains still were sensitive to polymixin B and to neomycin.[246]

Egyptian observers found chloramphenicol to be of benefit in early therapeutic trials for infantile gastroenteritis caused by Escherichia coli, but it failed later. Cross infection with chloramphenicol-resistant Strain O20

occurred. Unless bacteriologic control is observed, the use of antimicrobics, particularly chloramphenicol, may entail more hazard than help.[250]

Cholera

Cholera was more prevalent in India and southeastern Asia than in many years. Nearly 50,000 cases were reported, but many more unreported mild and serious ones, no doubt, occurred. The stated death rate, of nearly 50%,[251] is exaggerated. Mild cases seldom are counted or statistically included. Vaccine was used on a large scale, but its value is doubtful. There are better ways of prevention.

The rapid clotting of blood during cholera may account for thrombotic and embolic complications. Indian physicians noted a decrease in the prothrombin time, which remained low in some instances even after rehydration.[252] Other factors also play a role. The specific gravity of the blood often increased to 1.070, with a corresponding relative increase of corpuscular volume and viscosity, as noted in my experience.

Brucellosis

Patients or animals infected with Brucella often do not react to the dermal test as expected. The skin of infected guinea pigs usually was insensitive to an extract of Brucella, while their tissues reacted to it. The result of a skin test is no gauge of tissue sensitivity, and even that may not be demonstrable.[253] The observations are in harmony with the occasional failure of the skin of patients with brucellosis or of tuberculosis to react to brucellergin or tuberculin, respectively.

The occurrence of calcific aortic stenosis in several patients who had had disease, diagnosed in the past as brucellosis, suggested a relationship. Endocarditis occurs in chronic brucellosis, especially of the aortic valve, and calcification may follow.[254]

Debono found no therapeutic superiority of novobiocin over tetracycline.[255] Among 60 patients, tetracycline or streptomycin, or both had no effect on the duration of fever, or on bacteriologic and clinical recurrence.[255a] G forms of Brucella from microcolonies were virulent for mice. The significance of these minute variants in human infection is unknown.[256]

Tetanus

The prognosis of tetanus depends on the amount of toxin fixed in neural tissue before antitoxin is given; if large, no available treatment saves life. The best prognostic guide is not the length of time between the injury and the first sign but between the first sign and the first severe spasm. Antitoxin, in amount of 40,000 to 80,000 units intravenously, and 1,200,000 units of penicillin intramuscularly should be injected promptly. No further specific therapy is indicated; it only disturbs the patient.[257]

Antitoxic therapy of 100 patients in Nigeria did not influence the mortality rate significantly; nor did the severity of disease seem less after early treatment. There is no reason to assume that administration of antitoxin "will arrest the progress of tetanus, or, indeed have any beneficial effect."[258] This conclusion, no doubt, will disturb physicians who favor the therapeutic use of antitoxin. The management of respiratory stress is of great importance. It is uncertain whether hypertonia is relieved better by muscle relaxants or by central depressants.[259] Chlorpromazine and sodium amylobarbitone were used with success as sedatives.[260]

Clostridium tetani was found in the dust of a surgery and in 10 of 35 stools from normal people; yet no infection had occurred in nine years.[261] In another hospital, after the amputation of an infected arm, five patients had postoperative tetanus in a five-day period.[262] It is surprising not that tetanus occasionally occurs but that it is not commoner.

Chicken meat probably gave rise to poisoning by Clostridium welchii. The bacillus was present in the stools of 11 of 16 patients, and staphylococci, in 7, but, unfortunately, none of the flesh remained for study.[263] Canned pimientos were the source of botulism in 21 persons, of whom 12 died despite the use of antiserum.[264]

Tularemia.—Mice and rats fed on carcasses infected with Pasteurella tularensis contracted tularemia. Since rodents feed on carrion when other food is unavailable, tularemia may be propagated in nature by this manner in addition to other means.[265]

H. Influenzae Infection.—H. influenzae infects children oftener than adults, who presumably have immunity acquired from prior experience with the bacillus. Three adult patients were chronic alcoholics. Experiments suggested that alcoholism reduces resistance to infection,[266] as shown 40 years ago regarding pneumococci.

Diphtheria may injure the myocardium. In one instance, myocardial failure ended fatally 12 years later. An electrocardiographic abnormality had persisted, and at necropsy diffuse myocardial fibrosis was present.[267]

Melioidosis usually resembles glanders, but in one instance typhoid was suspected. There were diarrhea, splenomegaly, and arthritis, but none of the usual characteristics of glanders. Chloramphenicol, erythromycin, and cortisone failed to prevent death.[268]

Listeriosis occurred in a newborn infant. The mother had felt ill before delivery, and Listeria monocytogenes was present in her vagina. A sick dog may have been the source of infection.[269]

Infections by unusual bacteria were observed. A patient with pneumonia subsequently had meningitis and bacteremia due to a Gram-negative coccus identified as Mima polymorpha. Other cases of that infection were recorded with endocarditis,[270] bacteremia,[271] and meningitis.[272] An unclassified Gram-negative bacterium caused two outbreaks of meningitis among premature infants.[273]

Bacillemia.—Antimicrobic therapy reduced the incidence and severity of coccal infections, but serious diseases caused by drug-resistant Gram-negative bacilli have increased. Relatively benign infections have been converted into grave ones. The incidence of such infections was highest on the surgical service of a hospital. In 90% of cases, instrumentation of the urinary tract, cannulization of veins, injection of fluids, and paracentesis were implicated as inciting factors. Among 278 patients with bacillemia, a shock-like state occurred in 43, with a mortality rate of 65%. Chiefly involved were paracolon and colon bacilli, Aerobacter aerogenes, Proteus sp., Pseudomonas aeruginosa, and Salmonella sp. For therapy, the prompt use of an appropriate antimicrobic, vasopressor agents, and glucosteroids was recommended.[274] Of 106 septicemic infants, hemolytic streptococci were oftenest the cause before 1944. In after years, coliform bacilli predominated, and P. aeruginosa and hemolytic streptococci of groups other than A were common. The mortality rate was 72%.[275]

In a Festschrift for Prof. N. I. Nissen, Faber reported on 54 cases of bacteremia with E. coli. The portal of entry in 40 patients was the urinary or biliary tract; 5 followed a surgical procedure, and 4 had received steroid hormones. About half of the patients had other chronic disease, illustrating the invasion of relatively nonpathogenic bacteria in persons whose resistance is low.[276]

Four of nine patients with ulcerative colitis had portal bacteremia with P. aeruginosa, S. pyogenes var. albus, enterococci, or Escherichia coli. Bacteria were not present in the systemic circulation.[277] The results support a view that portal bacteremia in chronic or recurrent dysenteries may contribute to the development of hepatic cirrhosis.

Fever, a characteristic of leukemia, often is caused by infection, owing to low resistance of the host. Among 36 patients, 92 episodes of fever were observed. Fifty-nine accompanied infections mostly of the respiratory tract, pyelonephritis, and septicemia, with colon bacilli, staphylococci, and Bacillus pyocyaneus (P. aeruginosa). Fungi, especially Candida albicans, were recovered from 18 patients. Antimicrobics were helpful at times, but, because of the danger

of superinfection, long-term prophylactic therapy in leukemia is unwise. Fever also may result from the reaction to damaged tissue as part of the disease.[278]

The Staphylococcal Problem

Others share some of the opinions McDermott expressed in 1956, namely: staphylococci have not changed their characteristics and do not become resistant to penicillin during therapy; infections now are not more serious than before, and the greater incidence of infections in hospitals is in proportion to the increased number of complicated surgical procedures, intubations, hormonal and roentgen therapy, and other factors.[279] According to one observer, proof that antimicrobics increased the resistance of staphylococci generally has not been offered. The use of a few tons of antimicrobics can hardly have led to universal changes of any bacterium in its relation to man. Drug resistance may develop in special circumstances and involve small groups of persons. Contrary to much other evidence, staphylococci in the personnel of one hospital were more, not less, sensitive to penicillin than those found in patients. The relationship between the carrier state and "hospital" infections is not so close as has been stated. His minority opinion was based on results obtained by the accurate tube-dilution technique for testing sensitivity, not by the usual simpler but less reliable methods. Spontaneous variation, such as occurs among other microbes, probably takes place among staphylococci to account for changes in their invasiveness from year to year.[280] That such variation may occur was indicated in my studies[281] and in further unpublished ones.

In contrast with the views just cited, the importance of the problem is evident by the number of papers published on the subject, many more than can be cited here. Reports of a conference on staphylococcal infections appeared in seven papers, with editorial comment in the *Journal of the American Medical Association* on March 8, 1958, and a symposium of four papers appeared in the March issue of the *American Journal of Public Health.*

Staphylococcosis now is not only a menace to a community in which a hospital plays a malign role, but is indeed a universal problem, owing to the emergence and spread of antimicrobic-resistant cocci.[282] Type 80/81 cocci and those of Groups I and III comprised the majority of strains resistant to penicillin, streptomycin, the tetracyclines, and sometimes to erythromycin. Nearly all strains still were sensitive to bacitracin, carbomycin, neomycin, and novobiocin, but all resisted polymixin B.[283] Vancomycin, thiostrepton, and MK-111 were effective but are still under study.[284]

In a community under close control, 92% of persons had received antimicrobics during a five-year period, usually without need. Resistant staphylococci were isolated from 12.6% of persons who had not received antimicrobics for six months or had not been in contact with family members who had been treated. The percentage probably represents the prevalence of resistant staphylococci in communities where antimicrobics are widely used,[285] and this no doubt means almost everywhere.

Studies in Hospitals.—In one hospital, 41% of personnel were carriers of staphylococci. Only 4% were of Type 80/81, but these caused 69% of infections in patients. To reduce the hazard, the indiscriminate and routine use of antimicrobics for mild illness or in too small amounts when actually needed was stopped. Careful aseptic technique alone kept the incidence of surgical infections to less than 1%.[286] In another hospital, many patients acquired staphylococcal infections while receiving glucosteroids or antimicrobics. Four per cent of deaths were due to staphylococci, and in 14% they were a contributing cause.[287]

Nasal carriage of staphylococci was studied in nurses and laboratory workers. Of these, 59% were "true" carriers and 41% were occasional or noncarriers. After ex-

posure to the environment of the wards no change in the rates occurred, but for unknown reasons the cocci were displaced by penicillin-tetracycline-resistant Type 81 strains. The proportion of strains sensitive to penicillin fell from 71% to 13%.[288] Most nasal carriers of staphylococci also harbor them on their hands and clothes and transmit them to other persons by direct contact, by means of blankets or towels, or by dispersal into the air. The existence of non-nasal carriers must not be overlooked.[289] Improved ventilation in operating rooms alone failed to reduce the incidence of infections.[290] Bedside carafes,[291] oxygen therapy apparatus,[292] soiled laundry, laundry chutes, and refuse also contained resistant staphylococci.[293]

In Holland, an increased nasal carrier rate of antimicrobic-resistant staphylococci among patients in hospitals was due to an exogenous colonization by resistant "hospital" staphylococci, not by mutation in the patient himself. The pattern of resistance of the strains was determined chiefly by the nature of the staphylococci present in the hospital. Colonization occurred by preference in patients who received antimicrobic therapy. After they left the hospital, the carrier rate lessened and returned to normal in 6 to 12 months. Patients transmitted resistant staphylococci to about 11% of family members at home,[294] a figure close to that of Nolen's.[285]

Thirty-two outbreaks of staphylococcosis in English maternity hospitals were reported.[295] Novobiocin did not prevent infection or stop the carrier state during an epidemic elsewhere. Erythromycin eliminated staphylococci only while it was given.[296] In another instance, a nurse was the source of staphylococcosis. After her removal from service, the epidemic ceased without the use of antimicrobics.[297]

In the surgical wards of a hospital, eight cases of staphylococcal diarrhea occurred and five ended fatally. The patients had been treated with antimicrobics, and in each case the cocci were resistant.[298] Staphylococcal parotitis, regarded as a vanishing postoperative complication, seems instead to be increasing in incidence.[299] Seven instances were described.[300] Staphylococcal pneumonia in 75 infants and children had a mortality rate of 12%.[301] The gravity of the general problem led the American Hospital Association and others to propound recommendations for its control in hospitals.[282,302]

Seventy-four per cent of 27 victims of staphylococcal endocarditis died. One-third of the patients had had no known preceding valvular disease. Failure of therapy was charged chiefly to delay in diagnosis and treatment and to antimicrobic-resistant cocci.[304] Dosage as high as 140,000,000 units of penicillin has been used for staphylococcal endocarditis. Four of six patients treated with vancomycin for 14 to 28 days recovered, but one died later of heart failure and the other from the infection. The drug caused phlebitis, dermatitis, and deafness.[305] Two patients treated with large amounts of antimicrobics were superinfected with C. albicans. One died, and the other recovered after treatment with myocostatin.[306] Staphylococcal thrombophlebitis and septicemia resulted from polyethylene tubes in the veins of three patients.[307]

S. pyogenes var. albus can be pathogenic, especially in patients whose resistance is impaired by chronic disease, old age, surgery, or other factors, as illustrated in nine described cases. A survey of 40 cases revealed a death rate of more than 50%, similar to that from S. pyogenes var. aureus infection. S. pyogenes var. albus was harmless for mice, and passage in these animals failed to increase virulence.[308] S. pyogenes var. albus is a variant form of S. pyogenes var. aureus and may be mistaken for Gaffkya tetragena.[281]

Therapy.—Because of the variability of staphylococci to resist antimicrobics and the many disappointing results of treatment, there is no current uniformity of therapeutic advice, except to evacuate pus, if present, surgically. Different authorities recommend different antimicrobic regimens as follows.

In one laboratory, the pattern of sensitivity of staphylococci had not changed for 18 months. One-third of the strains were inhibited by 5 units of penicillin and 50% by 50 units. Tetracycline and novobiocin were effective against only 25% of strains. Penicillin therefore continued to be of value in 50% of infections. In severe cases, 20,000,000 to 40,000,000 units daily were recommended, together with erythromycin or chloramphenicol, when indicated. Oleandomycin had no advantage over other agents.[309]

Infections caused by cocci susceptible to 0.15 units per milliliter of penicillin require 1,000,000 units a day for a long period. When cocci resist larger amounts, treatment with 2 gm. of erythromycin and 2 gm. of chloramphenicol daily by mouth is needed. In some patients, bacitracin also was given in doses of 75,000 to 100,000 units a day, but the combination of three drugs was not more effective. Bacitracin caused renal disturbance. For localized infection, treatment with single agents, either erythromycin, chloramphenicol, or novobiocin was advised. No new agents have exceeded the value of penicillin before resistance to it developed.[310]

Because resistance to erythromycin and novobiocin evolves rapidly, these should be reserved specifically for infections not influenced by other agents. Cocci resistant to erythromycin also resist chloramphenicol. A combination of erythromycin and novobiocin is recommended for therapy at present. Evidence of cross resistance has not appeared. Vancomycin, ristocetin, and kanamycin are antistaphylococcal but may cause serious toxic effects.[311]

Minor furuncles or boils with no surrounding reaction or systemic symptoms need no antimicrobic treatment. Abscesses with cellulitis responded well to erythromycin or antimicrobic E 129, as compared with untreated ones. A short course of seven days of therapy did not induce drug resistance but did not prevent recurrences.[312]

Two papers contain helpful advice in selecting the appropriate therapeutic agent or combination of agents[280,282] and a table for guidance when resistance to one agent or another develops. Neomycin, nitrofurantoin, vancomycin, chloramphenicol, novobiocin, and erythromycin, in that order, had the greatest antistaphylococcal action. If a combination is used, neomycin and vancomycin or nitrofurantoin theoretically are most effective, but their toxicity must be considered. Narrow-spectrum agents should be used to avoid the emergence of other resistant bacteria, but wide-spectrum ones, at times, may be needed.[280]

Streptococcal Infections

In a two-month period, 11 family members had streptococcosis. Seven had sequels: one of cervical adenitis and otitis, two of arthritis, and four of nephritis. Type 1 streptococci, like Types 4, 12, and 25, were nephritogenic.[313] Two outbreaks of nephritis caused by Type 12 streptococci were observed in England. In one outbreak of 53 cases, 49 followed sore throat or otitis. Some children had symptomless hematuria.[314,315]

Subacute bacterial endocarditis occurs oftener in elderly patients than is generally believed. The clinical picture in 10 cases was misleading, and the only constant sign in 3 patients was a cardiac murmur.[316] In Dormer's series of 51 patients of all ages, treated with antimicrobics, 43% died. Exodontia preceded the onset of illness in 11 cases. The over-all immediate mortality rate among 82 patients was 25%, and a late recurrence affected 18%.[317]

Successive infections at 15- and 40-month intervals in a patient were caused respectively by S. pyogenes var. aureus, viridans Streptococcus, and Streptococcus faecalis. Erythromycin, penicillin with chlortetracycline, and penicillin with streptomycin controlled the separate episodes.[318] Subacute bacterial endocarditis treated with penicillin for 28 days resulted in relapse, uncontrollable infection, or death in 11% of patients. Treatment of 35 patients for 14 days with penicillin and dihydrostrepto-

mycin led to cure or probable cure in 91%. Relapse in 10% required the establishment of routine therapy for 21 to 28 days. No significant increase of resistance was encountered even during the relapses.[319]

Finland reviewed the status of therapy of all kinds of endocarditis.[320]

Rheumatic Fever

The behavior of rheumatic heart disease was observed in 757 children who had reached the age of 20 and were followed to ages up to 52 years. Acute carditis, polyarthritis, and chorea occurred in 33%. By the age of 20, cardiac enlargement was moderate in 80% and severe in 20%. Mitral insufficiency was present in more than 50%, and mitral stenosis and insufficiency, in 33%. Seventy-eight patients died: fifty-three from cardiac failure, eight from endocarditis, and seventeen from other causes. The over-all mortality rate was 8.3 per 1,000 per year for patients of 20 to 52 years, as compared with 16 per 1,000 for those less than 20 years of age and 3.1 per 1,000 for the general population. The survival curve for all patients showed that an estimated 82% would live to 45 years of age, as compared with 95% for the general population. Only 50% of patients with aortic and mitral lesions lived 40 years.[321] In further study of 385 of the children, the residual cardiac damage sustained before the age of 20, especially the degree of cardiomegaly, appeared to be the major factor influencing morbidity in the years 30 to 50.[322]

The course of rheumatic fever in 132 sailors was observed for 10 years. Diagnosis and treatment were established earlier than usually is possible. Even then, while therapy favored a more benign course, it did not reduce the incidence of valvulitis significantly. Valvulitis usually started too early in the disease to be prevented. It seems that no current therapy protects the endocardium from injury. There was no need for prolonged rest in bed.[323]

The incidence of rheumatic fever declined in New York City. The chance of recurrence fell from one in four before 1944 to one in seven after 1944 among children between the ages of 6 and 13 years. The change was attributed to improvement in the general standard of living. The initial decline antedated the antimicrobial era and decelerated no faster after antimicrobics began to be used for therapy and prophylaxis. Recurrence rate in the poorest economic group was unchanged.[324]

Active rheumatic disease may persist for decades in the absence of evident streptococcal infection. No virus grew in cultures of auricular appendages excised during commissurotomy.[325] On the other hand, Russians isolated a cytopathogenic virus from the blood, throat, and endocardium of patients. Neutralizing antibody was said to appear in the blood, and rabbits inoculated with the virus had lesions like those of rheumatic fever.[326] The observations need confirmation. The virus may have been commensal.

Literature on rheumatic pneumonia was reviewed.[327]

Prophylaxis.—Divergent shades of opinion persist about the success of controlling hemolytic streptococcal infection to prevent rheumatic fever. In one study, a single injection of benzathine penicillin given to 19,000 naval recruits reduced the number of infections, and the incidence of rheumatic fever was three times lower than in untreated ones. Prophylaxis failed in infections present before the program was started, during the later weeks of the recruits' training, and after they left the area. Protection at best lasted about three and one-half weeks. Untoward reactions occurred but were not serious.[328] In the next year, dosage of 1,200,000 units had no advantage over the smaller one but the incidence of infections was the lowest ever at the station.[329] In another study, 1.3% of treated persons had reactions to penicillin, usually of the serum-sickness kind. Illness often was prolonged, with relapses for more than a month. Antihistaminic therapy had but slight effect.[330]

A mass project was conducted for three years to reduce the incidence of streptococcosis and rheumatic fever among 6,460 school children. All students with colds or sore throat were inspected daily. If hemolytic streptococci were present, the child was sent home and treated with 600,000 units of benzathine penicillin intramuscularly. Only three cases of rheumatic fever accrued. If, as assumed, 3% of untreated streptococcal infections incite rheumatic fever, from 18 to 27 cases would have been expected.[331] The figure 3% is exaggerated; 1% or less is closer to actuality. None of 835 soldiers had rheumatic fever after three epidemics of streptococcal pharyngitis.[332]

An attempt made to abort an epidemic of streptococcal infection among school children with schemes of penicillin therapy, previously reported to be effective, was not entirely satisfactory. A large proportion of children retained streptococci, many of Group C, after 10 days of treatment. The school was the source of the epidemic, and families were secondarily involved. Adults seldom were carriers and seldom were infected.[333]

Disappointing results were noted by other investigators. More than 400 sibling contacts of 257 children with streptococcal infection were divided into three groups and treated prophylactically for five days with penicillin or sulfadiazine or a placebo, respectively. No difference was found in the rates of infection. Many children who received antimicrobics subsequently became infected—but usually with streptococci of a different type. Instead of trying to prevent infections, it seemed wiser to await actual evidence of infection and use full therapeutic dosage.[334] A general practitioner withheld antimicrobic therapy in about 1,000 cases of tonsillitis and otitis media until there were indications for its use. By his criteria penicillin was applied chiefly, and broad-spectrum agents occasionally, in only 25% of patients. The results in both treated and untreated patients were satisfactory. No complications occurred, but relapses were common. He concluded that a very large proportion of such patients need no treatment.[335]

Of 5,000 patients treated with antimicrobics for hemolytic streptococcal infections, 76 got rheumatic fever, in some instances in a few hours after the coccal infection. This and the fact that therapy did not eradicate all streptococci and that reinfection with a different type of streptococci may occur are reasons for prophylactic failures.[336] Prophylaxis with penicillin in patients with cardiovalvular disease is not as harmless as generally is thought. In 32 adults, so treated for an average of 14 months, 6 had allergic reactions, including 1 case of fatal anaphylaxis, 2 of "serum disease," and 3 with a generalized pruritic eruption.[337] Penicillin eliminated streptococci in children but depressed their specific immunity. Persistent carriers developed anti-M antibody oftenest.[338]

Therapy.—In a paper entitled "A New Approach to the Treatment of Rheumatic Fever," one looks in vain for something new. Acetylsalicylic acid given alone to one group and with huge doses of penicillin to another caused a similar degree of improvement in both. Penicillin had no effect on rheumatic fever but led to a diminution in the incidence of chronic heart disease,[339] as is believed by others. Americans annually consume 12,000,000,000 tablets of acetylsalicylic acid, or 6,000 tons.[340]

Mycoses

Histoplasmosis.—Histoplasmosis involved 19 persons who excavated a cellar. The incubation period varied from 7 to 16 days after exposure to dust. Six were severely ill; six were moderately ill, and seven mildly so. Histoplasma capsulatum was demonstrated in samples of the soil. Treatment with amphotericin B gave no significant result.[341] The drug seemed to be of value in treating hamsters infected with H. capsulatum.[342] The clinical spectrum of histoplasmosis from mild disease to pulmonary cavitation and fatal dissemination was outlined.[343,344] In a review of knowledge of histoplasmosis, interest in the possible thera-

peutic value of sulfonamides was revived.[344]

A survey of 22 sanatariums for tuberculosis in 15 states, revealed about 6% of the inmates to be sensitive to yeast-phase antigen of H. capsulatum.[345] Doubtless a number of positive reactors did not have histoplasmosis, but, since 10% to 20% of patients with histoplasmosis do not react to the antigen, the figure probably is balanced. Examination of resected pulmonary granulomatous tissue from 140 patients revealed tuberculosis in 81%. Fungi were present in the rest, H. capsulatum accounting for 16. Four patients had both tuberculosis and histoplasmosis.[346]

According to the results of skin tests, histoplasmosis and coccidioidomycosis are nonexistent in the Middle East, except in some persons who had been infected in the United States.[347]

Single macrogonidia, microgonidia, and a mycelial fragment were sufficient to infect mice.[348]

Coccidioidomycosis.—Pulmonary cavitation occurs in about 0.1% of known infected persons. Among 77 patients, the skin reacted to coccidioidin in only 57%.[349] Diagnosis in a case of disseminated disease was made after finding multiple minute granulomas and spherules of coccidioides immitis by hepatic biopsy.[350] A patient with severe coccidioidomycosis improved greatly after two weeks of therapy with amphotericin B, and the lesions healed in three months.[351]

In two of three patients with pulmonary actinomycosis, erroneous diagnosis of cancer led to surgery. Fan-shaped shadows or lobulated consolidation at the hilum extending along the bronchi, with lesions elsewhere in the lung were visualized roentgenographically.[352]

Amphotericin B was reported as having curative effects in a number of patients with meningitis caused by Cryptococcus neoformans.[353-355] It is believed generally that attempts to induce artificial immunity against fungi and yeasts are futile; yet studies suggested the value of an antiserum for C. neoformans.[356] C. albicans seemed especially to be responsible for some forms of stomatitis, but this and other fungi resided in 66% of normal mouths, as compared with 85% of diseased ones.[357] Perhaps they are mere saprophytes, occasionally pathogenic in debilitated persons.

Reports of 34 cases of mycotic endocarditis were gathered. Chiefly implicated were Candida, Blastomyces, Coccidioides, Aspergillus, Cryptococcus, Histoplasma, and Mucor. In some instances, endocarditis was incidental to generalized disease; others behaved like subacute bacterial endocarditis.[358]

Progress in the treatment of mycotic diseases, as reported in a review of 443 papers, leaves much to be desired. Some of the new antimicrobics, like amphotericin B, nystatin, and 2-hydroxystilbamidine, seemed to be of value for histoplasmosis, coccidioidomycosis, cryptococcosis, moniliasis, aspergillosis, and blastomycosis; penicillin in large doses, for actinomycosis, and sulfonamide compounds combined with antimicrobics, for nocardiosis. Iodide therapy, an example of mumpsismus in mycotic disease, was advised for geotrichosis and mucormycosis for which no other is of value.[359] Amphotericin B should be given intravenously and untoward reactions often occur.[360] Extracts of several fungi dissolved plasma clots and fibrin.[361]

Venereal Diseases

According to King, the reduced incidence of veneral diseases since 1945 probably owed more to better economic conditions than to new remedies. Antimicrobic therapy arouses false confidence and tends to weaken other measures for control. Syphilis declined in incidence, but since 1955 the number of new cases ceased to fall. There is no evidence that penicillin, given for syphilis or for other diseases, caused the decline in mortality from late syphilis. The incidence of chancroid in England diminished since 1955, but that of gonorrhea increased. Penicillin-resistant gonococci have loomed.[362]

Syphilis, in Massachusetts, rose by 9% over 1957. As reasons therefor, Fiumara

cited better reporting of cases, overconfidence in penicillin, a decline of moral standards after three wars, prosperity and too much leisure, apprehension of the future, increased consumption of alcohol, increased freedom of women, and the lowered standards of decency in literature, entertainment, conversation, and daily social relations. As a result, prostitution has diminished. "The rewards of virtue still have a tangible quality."[363] Review of 243 papers about syphilis appeared in these ARCHIVES.[364]

According to a theory, bejel is an infection intermediate between yaws and syphilis. By evolution, endemic yaws in the tropics spread to the Middle East and became nonvenereal syphilis or bejel. Then, as civilization followed, the treponemes gradually came to be spread by venereal contact, hence causing what is now known as syphilis.[365]

Gonococci.—Of 200 strains of gonococci, 38 needed more than 0.13 units of penicillin to stop growth. Infections caused by such strains often relapsed after treatment.[366] Evidently gonococci vary in sensitivity to penicillin and to streptomycin. Finland found no significant changes in the sensitivity of strains of gonococci to antimicrobics in recent years.[367] Others feel that resistant strains have appeared.[362] Penicillin failed in the treatment of 30 of 148 soldiers.[367a] Perhaps therapy with one agent should be replaced after a time with another in order to avoid development of resistance.[368]

Other Diseases

Leptospirosis.—Leptospira ballum inhabits many species of rodents. Foxes, raccoons, skunks, and wildcats also are hosts.[369] In a laboratory containing a colony of mice, 8 of 58 workers were infected. Four had febrile illness with orchitis.[370] Treatment of 14 patients with oxytetracycline shortened the average duration of disease to five days, as compared with nine days in 16 untreated ones. Renal and hepatic damage was not influenced by therapy.[371]

Multiple Sclerosis.—In last year's review, a spiral organism was mentioned as a cause of multiple sclerosis. A similar one was isolated from more patients,[372,373] but another idea turned up. Russians reported the therapeutic success of a vaccine prepared from the brains of rodents infected with E. H. A. virus derived from a patient with encephalomyelitis. They also found antibody against E. H. A. virus in patients with multiple sclerosis. Irish physicians were unable to confirm the results. The microbe had the characteristics of rabies virus.[374]

After many failures to incriminate African wild animals as sources of sleeping sickness, Trypanosoma rhodiense finally was isolated from a bushbuck.[375] Raccoons in Maryland harbored Trypanosoma cruzi.[376]

Typhus.—Of 318 Polish-born persons resident in England, nearly one-third had had typhus many years before and 45% of them still had specific complement-fixing antibody in their blood. Of those who escaped known infection, about 10% had the antibody. None was found in native Britons. Brill-Zinsser disease is expected to appear occasionally.[377]

Q-Fever.—Marmion reviewed knowledge of the ecology of Q-fever. It is widespread in Great Britain, where sheep and cattle are directly or indirectly the main sources of Rickettsia burnetii. Infection in small animals and birds, as found elsewhere in the world, was not detected.[378]

Toxoplasmosis.—The surprising number of 110 cases of toxoplasmosis, mostly in infants and children, were diagnosed in a six-year period in England. Inapparent infections were detected among family members of patients. The clinical manifestations varied greatly; some victims were asymptomatic; others were ill for months. Because lymphadenopathy was the chief manifestation of acquired toxoplasmosis, it often resembled infectious mononucleosis and characteristic leukocytes were present at times, but no heterophil antibody devel-

oped. Some cases, diagnosed as mononucleosis, actually are of toxoplasmosis.[379] Fatal congenital toxoplasmosis in an infant led to the discovery of the parasites in ducks, chickens, pigeons, cats, and mice in the vicinity. These probably are sources of human infection.[380] The subject was reviewed by Feldman. In a decade, toxoplasmosis emerged from being a rare entity to one of importance. Its mode of transmission is unknown.[381]

Leishmaniasis also may be manifested only by swollen lymph nodes. Three of four cases, observed in soldiers who had served in Cyprus and Malta, resembled sarcoidosis. Treatment with a compound of antimony was effective.[382]

Amebiasis.—Despite the popularity of chloroquine for the treatment of amebic abscess of the liver, emetine still seems preferable. Of 19 patients treated with emetine, all responded well, without toxic effects or relapse. Of 16 treated with chloroquine, 2 failed to improve and 4 had a recurrence within six weeks.[383] Erythromycin was even less effective.[384] As shown previously, amebas inoculated into germfree guinea pigs failed to cause lesions unless bacteria also were present. If the analogy applies to man, amebiasis is the result of symbiosis of Entamoeba histolytica and bacteria; neither is pathogenic alone.[385]

Clonorchiasis, endemic in the Far East, was encountered eight times in New York City. The infection in some persons was inapparent with or without eosinophilia; others had hepatalgia, and a few had obstructive jaundice and pancreatitis.[386]

In a fatal case of tropical eosinophilia or eosinophilic lung, numerous ascaris larvae were seen in the pulmonary tissue.[387] Ascaris, other unidentified nematodes, and microfilaria probably are causes of the disease.[388]

It comes as a surprise to learn, from European physicians, that the bacillus misnamed Pasteurella pseudotuberculosis is a cause of mesenteric adenitis. In a three-year period, 117 cases were so diagnosed, mostly by serologic tests. Cross reactions may occur with Salmonella.[389] It is of importance to see whether Pasteurella pseudotuberculosis actually is a cause and if the disease described occurs unrecognized elsewhere.

In seven instances of acute appendicitis, conservative treatment supplanted excision in the absence of adequate surgical facilities. Therapy with penicillin and streptomycin controlled the infection, and appendectomy was performed days later.[390] Perhaps cure may have occurred without excision. On the other hand, therapy may mask symptoms and result in various complications.[390a]

Chronic Bronchitis.—Tetracycline, administered continuously for 6 to 12 months, was said to have increased the rate of improvement and reduced the number of exacerbations of chronic bronchitis, as compared with untreated patients. No toxicity, drug resistance, or moniliasis was noted.[391] Subjectively, patients coughed less and had less sputum, but no objective improvement occurred.[392] In other treated patients, antimicrobic-resistant staphylococci appeared in the nose and feces.[393]

The concept of chronic infection of the lower respiratory tract needs revision. Etiologic diagnosis usually rests on the results of cultures of sputum or of aspirated bronchial exudate, but the bacteria that grow oftenest represent the normal flora. Cultures made post mortem are unreliable, owing to contamination of the area soon after death. In one study, sputum yielded the greatest number of bacteria; aspirated bronchial exudate, fewer, and the least were found in direct bronchial cultures made during thoracotomy. The bacteria most frequently found were Streptococcus, Staphylococcus, and Neisseria. No pyogenic bacteria were cultured from excised pulmonary or pleural tissue, except from one abscess. Evidently both in health and in chronic bronchitis, the lower respiratory tract rarely harbors pathogens, certainly not as often as the results of cultures of sputum or bronchial aspirates indicate. This being the case, it is easy to understand the failure

to cure chronic bronchitis or bronchiectasis with antimicrobics. Bacteria play little or no role in chronic bronchitis caused by tobacco smoking or other irritants.[394]

The rare condition called Reiter's disease was diagnosed in 185 patients; only 3 were women. Repeated attacks befell 104, sometimes for 20 years. Eighty-seven had arthritis only, and ninety-eight had ocular and dermal involvement.[395] In view of the uncertainty of diagnosis, one wonders if all 185 patients had Reiter's disease?

Steroid Hormones.—Corticotropin and hydrocortisone added to penicillin suppressed the inflammation and hypersensitive reaction to pneumococcal meningitis in 12 patients. The median duration of fever was 36 hours; only one died, and no harmful effects ensued in the others. Fear that adrenal steroids always are harmful in the treatment of infections is based on lowered resistance to latent infection and its rapid dissemination, as observed after the use of massive doses for long periods without antimicrobic therapy.[396] Cortisone and corticotropin lessened the severity of trichinosis in 15 patients. A rebound of symptoms occurred in nine of them after treatment ceased.[397]

The beneficial effect of steroid hormones in infections is not as promising as some authorities aver. Many reported favorable impressions of therapy were unsupported by convincing evidence. Before judgment can be rendered, it is necessary to include data on *all* patients treated, not only the good responses. Several complete reports cited in an editorial did not justify enthusiasm for therapy even for conditions in which it seemed to be indicated.[398] For some patients with meningococcemia or tuberculous meningitis, the hormones either had no effect or a bad effect. In other instances, of course, hormonal therapy may be life saving, but this is unpredictable. Perhaps the synthesis of new agents will provide better results.[399]

Catheters.—The case against the urethral catheter, as emphasized in last year's review, was summed up editorially.[400] Routine intubation to obtain "clean" samples of urine for diagnosis was condemned. There is no assured method to avoid forcing bacteria into the bladder and most of the cultures of catheterized specimens represent urethral contamination. When few bacteria are present, specimens of urine obtained by suprapubic needle aspiration of the distended bladder gives the most accurate information.[401] Overt cystitis followed four times in 100 catheterized patients, but the incidence of inapparent infection is much greater. Bacilluria occurred in 95% of patients with indwelling tubes.[402] Bacteriuria persisted despite antimicrobic therapy, and resistant strains often appeared.[403] The inadequacy of present methods of treatment should prohibit unnecessary instrumentation.[404] Infection from indwelling catheters can be avoided by irrigation of the bladder with 0.25% acetic acid through a 3-lumen catheter.[404a]

Studies in the Arctic.—Eastern Arctic Eskimos had less natural immunity against various infections than those near settled communities. In serum samples of 9,000 natives, 10% had O and H agglutinins in low titer for most varieties of Salmonella. O agglutinin for Salmonella typhosa, and Salmonella paratyphosa B were present in 12% and 7%, respectively. Few had antibody for Brucella or Pasteurella tularensis. In samples from natives in some areas, almost all had high titer of antitoxin against Corynebacterium diphtheriae; in others none had measurable amounts. Agglutinin for Hemophilus pertussis was present in titers of 1:8 or more in 23%. Tests for syphilis on 192 samples seldom gave positive results.[405]

During an Arctic expedition, seven men had no contact with outside sources of infection for three months. Cultures made at intervals from the nasopharynx showed few changes. S. pyogenes var. albus and diphtheroids persisted, and Bacillus subtilis appeared in four, although present in only one initially. B. subtilis also appeared on the

skin of six members, and staphylococci persisted in five of six. Diphtheroids, N. catarrhalis, and G. tetragena disappeared from several. Two men, unwashed for three months, had no deleterious effects.[406] Perhaps those who read this may wish to withhold the information from children averse to soap and water.

So-called antiseptic solutions, such as cetrimide and benzalkonium (Zephiran), may contain viable bacteria, especially Pseudomonas. Serious infections and deaths have resulted from their clinical use.[407]

Fever.—Fever has been recognized as a manifestation of disease for 2,000 years; yet even now it is imperfectly understood. Thoughts on the cause of fever from infections were summarized, by Wood. Ostensibly, circulating microbic endotoxin acts on leukocytes and possibly on other cells and releases pyrogen. Pyrogen derived from neutrophils seems to be a major factor. It is of unknown composition, distinct from bacterial endotoxin and from pyrexin and pyrogenic polysaccharides extractable from normal body tissues. The substance excites the thermoregulatory center in the brain.[408]

There are other causes of fever, as revealed by studies of a case of periodic neutropenia. In this disorder, the formation of neutrophil cells is arrested periodically, but during the episodes there is fever. Pyrogen derived from polymorphonuclear leukocytes, therefore, did not play an important role in the febrile response; nor were neutrophils essential to the development of refractoriness to the toxic and pyrogenic effects of endotoxin derived from Gram-negative bacilli. Neutropenia did not interfere with the production of antitoxic and agglutinating antibodies.[409] The injection of etiocholanolone in normal persons caused fever and leukocytosis.[409a]

Antibodies.—According to editorial comment, antibodies apparently are not modified preexistent globulins but are made anew from an amino-acid pool in the body. Synthesis may occur in 30 minutes, but its mechanism is obscure. Specific nucleic acids from the nuclei of primitive splenic reticular cells may play a role. The cells then transform into lymphocytes or plasma cells and enter the circulation.[410] Single cells, derived from lymph nodes of rats immunized against Salmonella of two types, were grown in tissue cultures. Some cells continued to make antibody against one type; other cells, against the other type. Single cells created only one antigen at a time.[411]

Microbial Genetics.—The importance of DNA, or deoxyribonucleic acid, in the genetics of bacteria and viruses was summarized. Discoveries began after the fundamental work of Levene and of Avery, who demonstrated the role of DNA in the transformation of types of pneumococci. It appears that DNA is implicated in the transfer of traits from one strain of bacteria to another by means of virus. A new generation of virus may contain microbes that have the combined traits of two parent viruses. In other words, viruses can be crossbred to form different ones.[412] Résumés of intensive research in progress are contained in the "Rockefeller Institute Bulletin, Annual Report, 1956-1957." For their contributions in the field of microbial genetics a Nobel prize was divided among Beadle, Tatum, and Lederburg.

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Contributions of Basic Science to Modern Medicine

Plasma Glycoproteins, Mucoproteins, and Mucopolysaccharides

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The plasma glycoproteins, mucoproteins, and mucopolysaccharides have been considered important in the pathogenesis or clinical evaluation of many diseases. The literature on this subject has become confused, however, because of inconsistencies in terminology and interpretations of findings. A brief review of this subject, in an attempt to clarify present knowledge of the field, seems indicated.

The changes which occur in the plasma concentrations of the carbohydrates associated with the plasma proteins in various diseases and the present knowledge of the physiology of these compounds are of clinical interest. The relationship of some of these substances to carbohydrate compounds in the ground substance of connective tissue and to deposits found in several pathologic states also deserves review.

Definition of the terms used is necessary at the outset; the recommendations suggested by Winzler [1] have been used. Because of the variations in terminology in previous articles, it is necessary to consider the chemical method of analysis used in each study in order to be certain of the nature of the substance measured; therefore, a brief description of methods of measurement of the various substances is included.

Terminology

There are two groups of compounds containing both carbohydrate and amino acids, glycoproteins, and mucoproteins. In the *glycoproteins*, the carbohydrate units are linked to amino acids of proteins by stable chemical bonds, and separation of the two can be accomplished only by degradation of the molecule into its individual carbohydrate and amino acid components.[2] All of the serum globulins apparently contain carbohydrate residues and fit into this category. The term *glycoid* is used for glycoproteins containing relatively small amounts of carbohydrate (0.5% to 4% hexosamine). In other glycoproteins, the carbohydrate comprises a relatively large proportion of the molecule (over 4% hexosamine); the term *mucoid* has been applied to these latter compounds. The most frequently studied compound in this group is the *seromucoid*.

The individual carbohydrate units present in glycoproteins are as follows:

(1) Hexoses: Galactose and mannose are present in approximately equimolar amounts.

(2) Hexosamines: Glucosamine and galactosamine (hexoses with an amino group replacing the hydroxyl group on the second carbon) are present in all these compounds. An *N*-acetyl group is usually attached to the amino nitrogen.* The relative amounts of the individual hexosamines vary in different compounds.

(3) Fucose: This is a methylpentose (it can also be considered a deoxyhexose) which is present in the serum glycoproteins.

Submitted for publication Feb. 3, 1959.

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* *N*-acetylmannosamine should be listed as a third hexosamine present in glycoproteins in view of its presence in the sialic acid components of these compounds.[3] It may also be present separate from the sialic acid units.

(4) Sialic Acids: These are a group of complex sugars which are acylated neuraminic acids and are present in serum glycoproteins and in gastrointestinal secretions. It has recently been found that the hexosamine present in this sugar is acetylmannosamine.[3]

In the second type of compound containing both carbohydrate and amino acids, the *mucoproteins*, the carbohydrate is present in the form of polysaccharide, linked to protein in most instances by a hydrogen or salt bond [1,2]; these compounds can be split, freeing the polysaccharide moiety from the protein. The polysaccharide units in these compounds are usually referred to as *acid mucopolysaccharides*, the acidity being conferred by hexuronic acid. Hyaluronic acid is an example of this type of compound. In many acid mucopolysaccharides, the acidity is enhanced by sulfate groups, as in the chondroitin sulfates, heparin, heparitin sulfate, and others. Acid mucopolysaccharides are present in small amounts in serum.[4,5]

The individual carbohydrate units present in acid mucopolysaccharides and in the mucoprotein complexes which they form are as follows:

(1) Hexosamines: Glucosamine and galactosamine are present, usually acetylated.

(2) Hexuronic Acids: Glucuronic acid is the main hexuronic acid present in the acid mucopolysaccharides. Thus far, only one other uronic acid, iduronic acid, has been found in an acid mucopolysaccharide, chondroitin sulfate B.[7] This compound has been found to be excreted in large quantities in the urine in Hurler's syndrome [8]; thus far, it has not been reported to be present in serum.

Methods of Measurement

A. Glycoproteins.—Total Protein-Bound Hexose, Hexosamine, Fucose, and Sialic Acid: The carbohydrate components of the proteins are usually measured after precipitation with alcohol to separate them from the free sugar in the blood. Hexoses are measured by a variety of reagents, which form colored substances after conversion of the sugar to furfural by dehydration with sulfuric acid; anthrone, tryptophan, orcinol, resorcinol, and other compounds have been used in this determination.[2,6] Hexosamines are determined after hydrolysis and treatment with alkali and acetylacetone to give a chromogenic ring structure which reacts with Ehrlich's reagent, forming a pink color.[2,6] Isolation of the hexosamines on a resin column increases the specificity of this method.[9] The total protein-bound fucose can be determined with the use of cysteine.[6] The sialic acid present in serum can be measured with Ehrlich's reagent [2] or diphenylamine.[6]

The term "total protein-bound polysaccharide" has been used by some authors who measured the total protein-bound hexose [10]; since presently available evidence indicates that the carbohydrate units in this group of compounds are not linked together in the form of a polysaccharide but are dispersed throughout the molecule, this term is no longer being used. "Nonglucosamine polysaccharide" has also been used as a designation for results obtained by determination of hexose associated with the serum proteins; this term has the additional defect of ignoring the fact that other carbohydrate substances are present in addition to hexose and hexosamine.

Isolated Components: The methods most frequently used to fractionate serum glycoproteins are precipitation and electrophoresis. The fractions obtained by precipitation are quantitated by the amount of protein present (by a nitrogen or biuret determination or the use of the phenol reagent of Folin and Ciocalteu), by measurement of hexose or hexosamine content,[2,6] or by a turbidimetric procedure.[11]

One of the most frequently used methods of fractionation by precipitation is the isolation of seromucoid. This is done by removal of most of the serum protein by the addition of perchloric acid; the protein which remains in solution is the seromucoid, which can be precipitated by phosphotungstic acid. This fraction normally con-

tains about 10% of the total protein-bound carbohydrate. Unfortunately, most of the reports of studies of the seromucoid refer to it as "mucoprotein," a term now used to identify a different class of compounds (see above), and therefore the methods employed by authors who use this name must be carefully checked to determine the nature of the substance which has been measured. Seromucoid consists of several components; one is known as *orosomucoid* but has also been referred to as M-1, MP-1, and α_1 acid glycoprotein. It has been used to induce antibody formation to permit immunochemical measurement.[12] Purified orosomucoid has been found to be 40% carbohydrate.[1] Several other glycoproteins have been purified and analyzed; a list of these compounds, their composition, and appropriate references are given in the review by Winzler.[1]

Fractionation of glycoproteins by electrophoresis has been accomplished most frequently by use of filter paper or starch blocks as a supporting medium. Analyses of the filter papers have been done by staining one strip for protein and a parallel strip for carbohydrate. The starch blocks are usually cut into segments and eluted for chemical analyses [13]; filter-paper strips have on occasion been handled in similar fashion.[14-16]

B. Acid Mucopolysaccharides.—The acid mucopolysaccharides present in serum or plasma can be measured after they are separated from most of the protein and precipitated with protamine; the hexuronic acid content of this fraction has been determined with use of the carbazole reaction.[5] Isolation and chromatographic studies of the compounds in this fraction have revealed two components which are labile to hyaluronidase and stain metachromatically with toluidine blue. One component contains galactosamine and has the mobility of chondroitin sulfate [4,5]; the second component has not been identified with certainty.

TABLE 1.—*Normal Values for Carbohydrates Associated with Serum Proteins and Serum Acid Mucopolysaccharides* [5,8]

	Mg. %	S. E. M.*
Total protein-bound hexose	121	±2.1
Total protein-bound hexosamine	83.4	±4.1
Total protein-bound fucose	8.9	±0.6
Total protein-bound sialic acid †	60.	±3.1
Seromucoid ‡	12.4	±0.5
Total acid mucopolysaccharide §	277	

* Standard error of the mean.
† Diphenylamine reaction.
‡ As hexose.
§ As uronic acid, carbazole reaction.

Normal values which have been reported for each of these types of measurement are given in Table 1.

Changes in Disease

The concentrations of many of the carbohydrate-containing components of the plasma have been measured in a variety of disease processes. The types of studies which have been done can be grouped in several categories.

"Acute-Phase Phenomena."—Increase in the concentration of many constituents of the plasma has been known to occur in nonspecific fashion in almost all conditions accompanied by an inflammatory component and in many other pathologic processes. The substances which respond in this fashion have been collectively called "acute-phase reactants." Examples of proteins which show this phenomenon are the C-reactive protein, fibrinogen, and complement; clinically, the increase in the sedimentation rate of red blood cells is the "acute-phase phenomenon" most frequently tested. The alterations which occur during the "acute-phase reaction" have been attributed to tissue destruction [6,17] or tissue proliferation.[6,10]

Some of the acute-phase reactants are glycoproteins, and therefore alterations in the carbohydrate content of several protein fractions occurs in this nonspecific fashion (Table 2). For example, the total amount of protein-bound hexose of plasma has been shown to be increased in infections, burns, neoplastic disease, rheumatic diseases, preg-

TABLE 2.—*Average Levels of Glycoproteins Found in Various Diseases* *

	Protein-Bound				
	Hexose, Mg. %	Hexosamine, Mg. %	Fucose, Mg. %	Sialic Acid,* Mg. %	Seromucoid,† Mg. %
Active tuberculosis	204	211	13.9	178	24.4
Subacute bacterial endocarditis	167	144	10.9	102	18.1
Advanced cancer	195	203	14.2	142	33.
Parenchymatous liver disease	141	158	15.7	96	8.1

* Diphenylamine reaction.
† As hexose.

nancy, and other clinical states.[6] Similar nonspecific changes have been found in the total protein-bound hexosamine in "acute clinical stress" [9,14]; the total sialic acid and fucose associated with the plasma proteins show similar changes.[2,6] Electrophoretic and chemical separations of plasma proteins in these states have shown that the greatest increases in protein, hexose, and hexosamine occur in the α- and γ-globulins.[6,14-16,22]

The concentration of seromucoid has been found to be increased in the same clinical states in which the total amount of protein-bound hexose and hexosamine are elevated by turbidimetric analysis of the total amount of seromucoid [11] and by individual chemical analyses of the amount of protein, hexose, and hexosamine in this fraction.[6,15,18] The proportion of the total protein-bound hexose and hexosamine found in the seromucoid fraction is usually increased in those sera which show an increase in seromucoid; this indicates that the increase in seromucoid is proportionately greater than the increase in the other glycoproteins during the "acute-phase" reaction. The orosomucoid component of the seromucoid has been shown to be elevated in cancer and rheumatic fever.[12] The protein content of the seromucoid has been found to be lowered in parenchymal liver diseases, hypopituitarism, adrenal insufficiency, and nephrotic states.[6,18,19] The fall in seromucoid in parenchymatous liver disease contrasts with the rise usually found in extrahepatic biliary obstruction; this has suggested usefulness of this measurement in the differential diagnosis of jaundice.[18]

The concentration of acid mucopolysaccharide in plasma has recently been found to increase in nonspecific fashion in several diseases.[20]

The alterations seen in diabetes mellitus, although qualitatively and quantitatively similar to the "acute-phase phenomena" may belong in a separate category. The total protein-bound hexose and hexosamine of the serum and the hexose and tyrosine content of the seromucoid fraction are elevated in diabetic patients with retinopathy, various arteriosclerotic complications, and the Kimmelstiel-Wilson syndrome. The total hexosamine seems to be the most sensitive index of the occurrence of such complications, provided other causes of an increase are excluded.[12] The clinical usefulness and significance of these tests deserve further study; the effect of the diabetic state itself on the metabolism of the hexose and hexosamine components of the serum proteins also is in need of additional study.

Other Changes in Individual Fractions.—Increases in the total protein-bound carbohydrate have been noted in clinical states characterized by marked increases in the concentration of individual serum globulin fractions. For example, the hypergammaglobulinemia of hyperimmunization,[22] sarcoidosis, and cirrhosis [15,16] can produce elevated total protein-bound carbohydrate levels. In these states, the change in the total protein-bound carbohydrate is usually due to the presence of large amounts of a globulin which contains the same ratio of carbohydrate to protein usually found in that globulin fraction in normal sera. The abnormal proteins found in multiple myeloma and macroglobulinemia also contain carbohydrate, and sometimes large increases in the total amount of protein-bound carbohydrate result. Laurell, Laurell, and Waldenström [23] have found that the abnormal

globulins of macroglobulinemia usually contain a higher proportion of carbohydrate than those found in myeloma.

A fall in total serum globulin can produce subnormal levels of protein-bound carbohydrate, as has been observed in nephrotic states[19] and starvation.[24] The same phenomen also may occur in agammaglobulinemia.

Changes in Relative Amounts of Carbohydrate and Protein in Individual Fractions.

Alterations in the relative amounts of carbohydrate and protein in individual serum glycoproteins have been observed and are usually expressed as changes in the hexose-protein or hexosamine-protein ratio. Payne, Shetlar, and co-workers have studied the ratio of total protein-bound hexose to protein, which they call the PR ratio.[25] This value for the PR is increased nonspecifically in many diseases in the manner of an acute-phase reactant. These workers have reported that the PR ratio, a relatively simple test to perform, is a useful guide to the severity of the inflammatory state and the effectiveness of suppressant therapy.[25] Since albumin contains very little or no carbohydrate,[2,6] the change in this ratio of total protein-bound carbohydrate to total protein often is the result of a fall in the concentration of carbohydrate-poor albumin and a rise in the absolute or relative concentration of carbohydrate-containing globulin.

The ratio of carbohydrate to protein in individual globulin fractions has also been studied. This ratio was not found to be significantly altered in the α_2-, β-, or γ-globulins, even when considerable increases in the amount of protein and carbohydrate in those fractions were present.[15,16] On the other hand, an increase in the total amount of seromucoid is usually accompanied by a rise in hexose-protein and hexosamine-protein ratios in that fraction.[6,15] It is of interest that the seromucoid is found in the α_1-globulin region by electrophoresis, and a rise in the proportion of hexosamine to protein in the various electrophoretic fractions has been found to occur only in the α_1-globulins.[15]

Treatment of patients with rheumatic diseases with steroid hormones results in a fall in the hexosamine-protein ratio toward normal in the α_1-globulin and seromucoid fractions, but no change in this ratio occurs in the other electrophoretic fractions.[15] These apparent qualitative changes in disease and their reversal with treatment are presumably due to alterations in the relative amounts of individual glycoprotein components of the α_1-globulin and seromucoid fractions which contain a higher proportion of carbohydrate than do the other components of those fractions.

Variations also occur in the relative amounts of the individual carbohydrate components associated with the serum proteins. For example, the concentration of protein-bound hexosamine increases proportionately more than the concentration of protein-bound hexose in several diseases.[6,26] This is additional evidence for the suggestion that individual glycoproteins can be selectively altered in disease.

The normal ratio of hexosamine to protein for the various fractions and the changes observed in certain disease states are given in Table 3.

TABLE 3.—*Average Hexosamine/Protein Ratios (× 100) in Serum Protein Fractions* [15]

	Total Serum Protein	Seromucoid	Globulin			
			α_1	α_2	β	γ
Normal	1.02	7.2	4.3	4.1	2.9	1.8
Rheumatoid arthritis	1.63	11.5	7.4	5.1	3.5	1.9
Rheumatic fever	2.06	9.5	6.9	4.5	2.8	1.6
Systemic lupus erythematosus	1.71	12.0	6.2	5.2	3.1	1.7
Pneumonia	1.76	9.0	8.7	5.9	3.6	1.6
Cirrhosis of liver	1.89	9.8	4.5	3.8	2.8	2.0

Physiology and Pathophysiology

There is considerable uncertainty about the physiologic basis for the alterations which occur in the carbohydrates associated with the serum proteins. There is evidence that the origin of some of these serum components is in the liver. In certain diseases the abnormal glycoproteins in the plasma are derived from pathological tissues. There is some doubt, however, as to the mechanism responsible for the changes in plasma glycoproteins observed in most diseases. The relationship of the carbohydrates associated with the plasma proteins to the carbohydrate components of connective tissue is another area of uncertainty at the moment.

There is both clinical and experimental evidence for the origin of some of the plasma glycoproteins in the liver. Experimentally, the increase in the glycoprotein content of rabbit serum which occurs following bleeding is prevented by the production of liver damage with phosphorus or benzene.[27] The fall in the concentration of seromucoid which occurs in patients with parenchymatous liver disease[18] is also cited as evidence for synthesis of this material by the liver. It is of interest that the protein content of the seromucoid falls to a greater degree than the hexose[26] and hexosamine[15] in this fraction, indicating that a change in the composition of the seromucoid occurs in patients with liver disease.[6] The fall in the concentration of seromucoid in parenchymatous liver disease can occur despite a rise in total protein-bound hexose; this apparent paradox is found when there is a considerable increase in the amount of γ-globulin, the rise in γ-globulin hexose counterbalancing the fall in seromucoid hexose.

The nonspecific elevation of glycoproteins found in so many diverse clinical states suggests the possibility that the pituitary-adrenal response to stress is responsible for this phenomenon. The decrease in seromucoid concentration observed in hypopituitarism and adrenal insufficiency[18] supports this concept. However, corticotropin (ACTH) and cortisone do not significantly alter the total serum glycoproteins or seromucoid in normal guinea pigs[28] or dogs,[29] and an elevation of total serum hexosamine in response to acute clinical stress has been observed in a patient with Addison's disease.[14] In addition, cortisone and corticotropin therapy cause a diminution in the elevated total glycoprotein and seromucoid levels which occur in various rheumatic diseases[6,9,14,15] and cause a return of the hexosamine-protein ratio toward normal.[15] The nonspecific alterations seen in various clinical states are, therefore, probably not due to pituitary-adrenal influences.

It has been suggested that an increase in the serum glycoproteins may arise by depolymerization of the ground substance of connective tissue and release of solubilized components into the circulation.[6,30] The finding that the connective tissue adjacent to tumors in mice contains an increase in extractable material with the properties of seromucoid has been quoted in support of this suggestion,[30] but this observation also might be explained by an increase in capillary permeability, producing exudation of plasma components into the area. Furthermore, the chemical differences between seromucoid and the acid mucopolysaccharides of the ground substance militate against a fundamental relationship of the two substances. The acid mucopolysaccharides of connective tissue contain uronic acid, whereas the seromucoid and other serum glycoproteins do not. A second chemical difference is the presence of polysaccharide moieties in the compounds in connective tissue, whereas the carbohydrate units in the seromucoid and other plasma glycoproteins are scattered throughout the protein, apparently as individual monosaccharides. It should be mentioned that neutral protein-bound carbohydrates of the type found in serum have been demonstrated in various body tissues; they contain mannose, galactose, methylpentose, and hexosamine.[31] These compounds are distinct from acid mucopolysaccharides in that they do not contain glucuronic acid.[32] The neutral pro-

tein-bound carbohydrate present in the connective tissue may be in equilibrium with plasma protein, and alterations in this material could contribute to changes in plasma glycoproteins in disease, but inferences concerning alterations in the metabolism of connective tissue based on changes in plasma components must be made with great caution.

Histochemical observations have shown the presence of abnormal materials staining for carbohydrate in affected tissues in many diseases. Since the exact chemical nature of these deposits has rarely been defined, definitive statements can not be made concerning their relationship to the glycoproteins present in plasma. Similar caution is necessary in interpreting results obtained by determination of glycoprotein components of serous effusions and spinal fluid unless the studies establish a chemical relationship to the components in the plasma. The abnormal deposits of carbohydrate material have been carefully studied in Hurler's syndrome and have been shown to contain two types of acid mucopolysaccharide, chondroitin sulfate B and heparitin sulfate.[8] Large quantities of these polysaccharides have been found in the urine, but no studies of plasma levels have been reported. In amyloidosis, the deposits are known to contain carbohydrate, but no relationship to protein-bound carbohydrate in plasma has been established.

The recent observation that plasma contains small quantities of acid mucopolysaccharides which are chemically similar to those present in connective tissue[4,5] gave hope that changes in this serum component might reflect alterations occurring in connective tissue. The lack of specificity found thus far in the alterations in concentration of these components in disease has been disappointing.[20]

Many substances with interesting physiological properties have been found to be glycoproteins. For example, a glycoprotein has been shown to have an inhibitory effect on the agglutination of erythrocytes by influenza virus[6]; an acidic α_2-glycoprotein is probably the thyroxin-transporting protein of serum[33]; many other physiologically important substances have been shown to be glycoproteins, including prothrombin, fibrinogen, gonadotropin, and the C′ 4 component of complement.[6] Since carbohydrate has been found to be associated with many diverse types of protein, the observation that a particular substance is a glycoprotein does not imply any necessary physiological relationship to other carbohydrate-containing substances. In most instances the finding of carbohydrate associated with a plasma component has indicated only that it is a globulin.

There are two other aspects of the physiology of glycoproteins which deserve mention, although at the moment they are merely at the horizons of our knowledge. One concerns the fact that carbohydrate units are interspersed among the amino acid units within the polypeptides of many proteins. This necessitates a redefinition of the concept of protein. Studies of the nature of the linkages involved and the intermediary metabolism of these compounds will be of interest. The second concerns the chemical relationship of some of the plasma glycoproteins to carbohydrate-containing compounds in gastrointestinal secretions. The presence of sialic acid in both types of compounds is of particular interest. Further understanding of the relationship of these substances also requires greater knowledge of details of chemical structure.

Summary and Conclusions

Initial knowledge of a field often raises more questions than it answers. The presence of carbohydrate units in association with plasma proteins is known, and information is available as to the types and amounts of monosaccharide units present. The concentration of these glycoproteins and mucoproteins in plasma increases nonspecifically in many disease states, in the fashion of "acute-phase reactants." Changes in the relative concentration of various components usually occur in these instances, indicating different degrees of response of individual

glycoproteins. In some diseases, such as myeloma, macroglobulinemia, and sarcoidosis, a single abnormal glycoprotein is found in the plasma in large quantities.

The relationship between plasma glycoproteins and abnormal carbohydrate components found in tissues in many diseases is uncertain in most instances because of lack of adequate chemical characterization. The value of plasma components in furthering knowledge of the physiology of the carbohydrate-containing compounds in connective tissue and intestinal secretions remains to be established. Further progress in the interpretation of the physiological significance of changes in plasma glycoproteins will be greatly aided by isolation, chemical characterization, and clinical studies of additional individual glycoproteins.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

The Sanctity of Life and the Criminal Law. By Glanville Williams, B.A., M.A., Ph.D., LL.D. Fellow of Jesus College, Cambridge, Mass. Price, $5. Pp. 350, with no illustrations. Alfred A. Knopf, Inc., 501 Madison Ave., New York 22, 1957.

Rarely does one find anyone these days courageous enough to confront head-on such problems as life, death, abortion, or euthanasia. The point of view of the author is that of a humane person, who happens to be a lawyer, rather than a strictly or even mainly legalistic approach to the innumerable problems which face man and society in the great complex maze of intertwining habits, motives, and practices which go to make up existence. This is an excellently written book, stripped largely of "legalese." It ranges over a great variety of problems which arise out of and contribute to the anxiety neuroses, which constitute one of the weightiest problems of our age. It is a book of philosophy, sociology, and religion as well as legal argument.

The difficult but important theme is simple. If men were free to follow their impulses of hatred and aggression, if they could murder at random and without punishment, society would promptly disintegrate. On the other hand, there are classes of murder or quasimurder which are prohibited by the ethical codes which have risen as part of the philosophic constructs of society rather than out of social necessity. Suicide, infanticide, and abortion are such forms of killing. All these are tough knotty problems, described best by that naughty word "controversial." What should be the legal and what should be the moral attitude toward birth control, sterilization, and artificial insemination? In a population increasing almost exponentially, these questions demand an answer. For the most part, this answer has been evaded by our society.

Glanville Williams' book consists of an expansion of the James S. Carpentier Lectures, given in 1956. It is a courageous book, and, despite the fact that the author might be accused of trespassing outside the lawyer's sphere, it is a scholarly, dispassionate, and highly critical discourse on questions which have to be faced. Morality can hardly be conceived of as existing apart from social and economic aspects of life. The history of man is not long enough and our knowledge not sophisticated enough to know all, or even many, of the forces which have determined the slow evolution of our attitudes and feelings which in turn govern and create moral and ethical principles. The connecting thread of the whole discourse is how human life, actual or potential, is or ought to be managed and protected under the criminal law of the English-speaking peoples in a society still constrained by the impulses, if not the doctrines, of Christianity.

The very nearly instantaneous halving of the death rate in many countries which suddenly utilized the protective measures of modern preventive medicine, the increase of the population of India by fifty million people in one decade, and the increase of the population of China by thirteen million a year illustrate the impossibility and futility of maintaining the religious theory that it is right to use every weapon of science to reduce the cruel and horrible natural checks on the increase of population but wrong for scientific methods to find substitutes for these natural checks. Surely, it is immoral to condemn hundreds of millions of unborn people to a substandard existence, which can lead only to starvation and savagery, on the strength of religious doctrines. Williams is at great pains to point out the background for his rejection of the doctrines of the Roman Catholic Church and what he sees as internal inconsistencies. This is no tightly argued legalistic quibble but a scholarly and realistic inquiry into some of the paradoxes resulting from too literal interpretation of documents or traditions which have been accepted as having divine authority.

Artificial insemination presents not only legal but social and personal problems of a kind which almost defy solution in our present society, but the lines along which a more satisfactory solution to these problems might occur are indicated. Edgar Allen Poe and all his

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macabre and morbid tales did not have to consider the approach to immortality which may be possible when frozen semen is used to procreate successive generations from female offspring. This approach to a genetic pure line is practicable now in certain domestic or experimental animals.

I follow the arguments and stand for the most part with Williams' formulations in the majority of his attitudes. Certainly he has a broad and humane point of view. Where it comes down to the direct practical application of some of his ideas, however, his philosophic attitudes present difficulties and indeed dangers. The problem of euthanasia, or the willful putting to death of a patient by a physician or a group of physicians, eventually may become accepted practice in the future, though, physicians being human, errors will be made. In Western Christian societies today, however, the effectiveness of physicians would drain off into chronic suspicion with great rapidity if patients knew it was an accepted practice for a doctor to decide the stage at which an individual life was no longer worth living. The descent into infamy by Nazi physicians has probably reduced not only the general appeal of the euthanasia movement in the population at large but any likelihood that it will be translated into effective action in our time. For, when the physician is judge, jury, and executioner, even if all three tasks are conducted with the motivation of a good Samaritan, a sick man would take little comfort in his fears that his doctor might be changing roles. Then, indeed, we will return to the times when the hospital was looked upon as the place to go to die rather than, hopefully, as now, a place to get well.

Regardless of what one believes and feels, Williams has written an honest, forceful, and moving book which faces some of the unattractive aspects of reality with candor and courage. Only thus can society advance under the combined influence of dispassionate reasoning based on sound facts and humane principles of morality and ethics.

WILLIAM B. BEAN, M.D.

Cold Injury, Ground Type. By Tom F. Whayne and M. E. De Bakey. Price, $6.25. Pp. 569, with 52 tables, 32 charts, and 105 illustrations. Superintendent of Documents, Government Printing Office, Washington 25, D. C., 1958.

The tragic mistakes and misunderstandings regarding the occurrence and the preventive measures required for the prevention of cold injuries are strikingly and unequivocally set forth in this volume of the medical history of World War II. It is, indeed, a tragic reminder of the failure of mankind to learn from previous bitter experiences. It can only be hoped that similar mistakes will not prevail in future years. Inadvertently this book can be considered as necessary reading for social scientists as well as practicing physicians and medical investigators.

Probably the outstanding lesson to be learned from the material in this volume is the necessity for continued research into the basic mechanisms of these disorders. As so often occurs, once the immediate problem has disappeared and urgency is a matter of no importance, research ceases. No single casualty factor in warfare has a greater impact on the fitness of combat units than this type of injury. The need for research is obvious. The Surgeon General, S. B. Hays, in his foreword to this volume, has concisely restated the information presented. He needs only add that by his efforts research is continuing.

Several questions remain unanswered to the reader of this treatise. There is a striking failure to explain the low incidence of cold injury in the Russian Armies and to point out that they had apparently learned their lessons from the Finnish War. Another and more serious objection lies in the inability of the authors to utilize statistical procedures to document their statement that the second year of the Mediterranean campaign resulted in a so-called improvement in cold injuries. The evidence presented would hardly lead the reader to agree with this conclusion.

There is no doubt as to the importance of this volume. It should be required reading for all new and present service medical officers. For command personnel of our armed services the requirement is also obvious. It may be well for the medical officers of World War II and the Korean conflict to devote a number of quiet evenings in retrospective reading and contemplation.

STEVEN M. HORVATH

Schizophrenia. By Manfred Sakel, M.D. Price, $5. Pp. 363, with no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1958.

Manfred Sakel introduced insulin shock therapy in 1927, only two years after his graduation from medical school. He began his work with drug addicts and quickly extended the therapy to

schizophrenics. When he reported that this most refractory of psychoses was favorably influenced by insulin therapy, he was greeted with skepticism and opposition. However, Poetzl, Director of the Vienna Psychiatric Clinic, took Sakel under his wing and gave him the clinical facilities to develop his method of treatment. In relatively few years insulin shock therapy was accepted all over the world as the treatment of choice for schizophrenia. It furnished the impetus for the introduction of Metrazol and electric convulsive therapies for mental disorder. It may also be given credit for facilitating the current upsurge of interest and activity in pharmacotherapy and biochemical concepts of psychosis.

In view of the tremendously important psychiatric developments which he initiated, Sakel's place as one of the truly significant figures in the field is assured. This fact will probably cause the readers of this volume to be disappointed. Much of the book is devoted to a description of the routine mental examination and the symptoms of schizophrenia. These add little to the treatment of these topics available in any standard text. The detailed description of insulin therapy should be valuable to those who still administer Sakel's treatment. However, the use of insulin shock has been diminishing rapidly in this era of "tranquilizers." One may speculate that the abandonment of insulin therapy might not have occurred so readily had Sakel's method, which involves close and constant medical supervision of the patient during treatment, been rigorously followed.

To Sakel the physiological and psychological changes induced by insulin were obviously fascinating. He seems to have observed and charted them with loving care, and, although he ascribed little importance to psychological factors in the etiology of schizophrenia, his patients must have received the optimum of emotional support.

It is likely that the major contribution of this volume will be historical. The personal account of an innovator in medicine rarely lacks interest, and this is no exception. To me, Sakel's account does not fully explain how he came to evolve an extremely complicated therapeutic procedure from a physiological hypothesis which borders on fantasy. However, this may represent the intuitive leap of genius, and genius has seldom been able to explain itself.

CHARLES SHAGASS

Protein Nutrition. By Fredrick J. Stare, M.D., Ph.D. Price, not given. Pp. 1066, with 54 figures and 51 tables. New York Academy of Sciences, 2 E. 63d St., New York 21, 1958.

This volume is the report of a conference on protein, with particular emphasis on human requirements. The conference was planned by the New York Academy of Sciences and made possible through the support of E. I. du Pont de Nemours and Company. The formal papers were presented by scientists with years of research experience and were essentially reviews of the researches of the various investigators on (1) the protein needs of man for various stages of the life cycle, (2) the incidence and characteristics of severe protein malnutrition in young children in many parts of the world, and (3) protein nutrition in terms of amino acids, including the problem of possible amino acid imbalance.

Each series of papers was discussed by leaders in the field. The discussions, which frequently were in direct conflict with the interpretations of the speakers, were not always as well documented as the original papers. In an area in which world food supplies and agricultural potential are of such significance for feeding populations, it is to be regretted that most of the available long-term studies on protein needs at all ages have been done in this country with use of subjects ingesting the high-animal-protein diet of the United States. Short-term studies quoted by the discussants would suggest a tremendous capacity in man to adjust to lowered protein intakes and to a limited intake of animal protein. Unfortunately, short-term studies provide little information on growth potential, longevity, productive capacity, or susceptibility of populations to disease as these factors might be influenced by protein nutrition. In the last analysis, standards of intake of any nutrient can only be measured in the capacity of that nutrient to sustain productive lives.

MARGARET OHLSON

A History of Public Health. By George Rosen, M.D., Ph.D., M.P.H. Price, $5.75. Pp. 551, with no illustrations. MD Publications Inc., 30 E. 60th St., New York 22, 1958.

Dr. Rosen has written a readable, persuasive, and provocative book. He ambitiously covers the outstanding developments in public health from antiquity to the present. Well organized and carefully indexed, it is an excellent reference for the student or professional.

Names, events, and dates are provided against a general historical backdrop that emphasizes changing socioeconomic patterns. The convincing presentation becomes provocative as current and future problems in public health are presented and discussed.

It would be difficult for the thoughtful reader not to be convinced that past events in public health are but prologue. Changing concepts of professional responsibilities and prerogatives, the function of government, and a more vocal beneficiary of public health services are obvious forces that will affect the future course of public health. As Dr. Rosen says:

"These developments must be seen, however, not alone as events peculiar to the United States but in the perspective of a worldwide historical evolution that has brought into being the modern state with its concern for individual, family and community needs for organized social security and service."

Within these widening horizons, Dr. Rosen sees a decreasing emphasis on many established programs, such as communicable disease, and increased emphasis on broader community health programs, involving such items as air pollution, radiological health, housing, population mobility, accidents, mental health, and chronic and degenerative diseases.

FRANKLIN H. TOP, M.D.

The Clinical Examination of the Nervous System. By G. H. Monrad-Krohn, M.D., F.R.C.P., Professor Emeritus of Medicine (Neurology) in the University of Oslo. Revised by the author with the assistance of: Sigvald Refsum, M.D., Professor of Medicine (Neurology) in the University of Oslo; Physician-in-chief in the Neurological University Clinic, Oslo. Price, not given. Pp. 466, with 173 illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33d St., New York 16, 1958.

The appearance of the eleventh edition of this book is evidence of its wide acceptance as a standard text with reference to the neurological examination. The book has become progressively longer with succeeding editions, which has somewhat reduced its value as an undergraduate textbook. The content is largely derived from the author's own clinical experience. There are sections on neuroradiology, electroencephalography, electromyography, and cerebrospinal fluid examination, which are brief and are more fully covered in other texts. There is little emphasis on the analysis of neurological signs in neuroanatomical or neurophysiological terms. The most valuable sections are those which deal with the techniques of the neurological examination and the clinical interpretation of neurological signs. The monograph is not intended to be a text on neurology, but it is especially valuable to the medical student for use as a preparation for clinical neurology and as a guide to the clinician interested in the details of the neurological examination.

H. HOUSTON MERRITT, M.D.

Ciba Foundation Symposium on the Neurological Basis of Behaviour. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $9. Pp. 400, with 109 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This symposium was held in London in early July, 1957, just prior to the meetings of the international congresses in neurological sciences, in Brussels. The London meeting, attended by some thirty-four persons, commemorated the centenary of the birth of Sir Charles Sherrington (1857-1952).

The symposium consisted of nineteen papers by thirty authors, presentations that ranged the field of neurophysiology, neurochemistry, and neuropharmacology. The book is largely a reviewing and a bringing up to date (summer, 1957) of observations and experiments that for decades have concerned some of the authors. Inherent in the technique of the symposium is much restatement, but the book will orient those who want to know about the modern neurophysiology, neurochemistry, and neuropharmacology. A feature of the book is the record of the seemingly free discussions that followed each presentation or related group of presentations. These discussions bring out the fascinating confusion in which some of the work now finds itself.

Electrophysiology forms the subject of the bulk of the papers presented in the symposium. As Klüver noted in his summary, at the termination of the three days, when Sherrington was over eighty he confessed ("Man on his Nature," New York, The Macmillan Company, 1941, p. 413), "the bald submission of some electrical potentials," as a contribution of neurophysiology to psychiatry, must appear "almost derisory." Although Klüver felt that this

symposium went beyond this juncture in its attempts to contribute to an understanding of normal and abnormal behavior, the Chairman (G. W. Harris) remarks, in his opening statement in the book, "The connexion between the work discussed in this symposium and practical psychiatry will probably seem remote," as indeed it does. Life behavior and elicited behavior are often enough very different matters. To discourage remoteness it might have been useful to have enlarged the group to include some persons, undoubtedly in the neighborhood at the time, who have been thinking about behavior in terms beyond the observation of conduct and reactions to stimulation. Their presence would have likely made the group less cohesive, but, as some who were present would be apt to observe, they may have been educable. One likes to believe that Sherrington in his wisdom would have included them.

Introducing his discourse on the temporal cortex, Penfield (p. 150) quoted Sherrington's remark, "It must be great fun to ask the 'preparation' a question and have it answer." Certainly it is great fun and a great privilege, just as it is to work in practically any area subsumed under the heading of medicine. It is an exacting task to formulate the realistic questions in research of the type reported in this symposium. On the questions asked, mainly depend the answers. An answer may be forced from protoplasm that has little relevance, if the cells be disturbed enough. All tissues, as all people, have their thresholds to physical or chemical stimuli. When, in addition, it is realized that the answer may be subject to the vagaries of interpretation, it is obvious that "behavior" is in danger of becoming what we make it.

I was interested to find in the book (p. 386) a concept of "keeping one's hands dirty," a method I have always advised for garnering clinical competence. Selig Hecht had used it long ago to symbolize the road to progress in science by which dedicated researchers, such as those who partook in this symposium, add to the slow accretion of knowledge. It does not detract anything from their hard work to garner the feeling—as the chairman of this symposium appears to have done—that their derivations seem rather remote from the later-day psychiatry.

These techniques for ravelling behavior are remindful of the manner in which some physicians of a former age became psychiatrists—by becoming neurologists. Over the years, it dawned on most people that a neurologist by reason thereof need know little more about behavior than does, say, an anatomist, obstetrician, or urologist and that to become a specialist in human behavior requires a considerable concentration on and study of the many, many reasons why people act the way they do. That microneurology will take us very much closer to the understanding of man's natural and unnatural behavior than did macroneurology is certain to be questioned. It is one approach among the many and probably not the main one. But any sincere approach is welcome, particularly if the sincerity be tinged with humor and humility.

As with other Ciba Foundation symposia, the book is nicely constructed, with type of comfortable reading size on nonreflective paper. The illustrations are clear; the index of ten pages is adequate.

The papers in this volume are by distinguished authors in the forefront of neurobiological research; included among others (besides those already metioned) were Bard, Dell, Eccles, Elkes, Gastaut, Jasper, Magoun, Olds, and Richter, and among the discussants were Adrian, Brain, Feldberg, Jefferson, Lewis, MacLean, and Williams. Here is an excellent summary of current thinking in neurophysiology, neuropharmacology, and neurochemistry.

CHARLES D. ARING, M.D.

To Work in the Vineyard of Surgery, The Reminiscences of J. Collins Warren 1842-1927. Edited by Edward D. Churchill, M.D. Price, $6. Pp. 288, with 3 illustrations. Harvard University Press, Cambridge 38, 1958.

This painstakingly edited and annotated autobiography, the memoirs of Dr. J. Collins Warren, gives concrete expression to the extensive contributions made by the Warren family over six generations to Harvard, Boston, and the American medical profession. Warren himself lived through the time of the application of ether to anesthesia, the vast expansion of surgery with the frightful mortality from infection before the advent of Lister, and finally the developments which occurred when infection and the fear of infection were greatly reduced by antisepsis and asepsis. The extensive and scholarly annotation and footnotes interrupt the narrative on nearly every page. They provide detailed background and much information valuable for those not familiar with medicine or medical history. Details of early medical education, Civil War surgery, extensive postgraduate training in the great medical centers

of Europe, and, finally, the productive career in practice and teaching at Harvard made up the bulk of the narrative. A deep reticence about personal matters, professional and family, make the book impersonal and somewhat mechanical.

The history of one aspect of American medicine is well illustrated. The development of relationships between hospitals, medical schools, and universities was radically different at Harvard and Johns Hopkins. The fact that there are many hospitals for clinical training, research, and patient care at Harvard in effect results in Harvard being many medical schools rather than one. Joint appointment in hospital and medical school with the title of head of a clinical department was a misnomer at Harvard. The head of a clinical department did not run the service in all the affiliated hospitals. On the other hand, administrative control of the direction of endeavor in The Johns Hopkins Hospital resulted from the fact that the head of a department in the Medical School also ran the clinical department as chief of service. This made for homogeneity as well as effective control of hospital policy and program by those who were directly responsible in their university appointment for the instruction in the medical school, the training of residents, and the forwarding of research. The remarkable thing is that either plan seems to work well as long as the people concerned are competent in their several roles as teacher, physician, and investigator. Cohesion, unity, and facility in organization and administration are easier to achieve where academic and hospital appointments unify the hospital and university functions of a medical school.

Another handicap, seen most clearly in its effect on the lives of individual clinical professors, has been the physical separation of basic scientists in medicine from their colleagues outside the medical school and the separation of the clinicians from the university itself. Regardless of all the efforts that may be made, geographical separation reduces or eliminates that essential intimacy of scholars in diverse disciplines which enriches the lives of those who have it.

In the book the continual interruptions of continuity in the many and massive footnotes could have been avoided if they had been set off from the body of the book in a repository in the back. Much of their meat has great historical interest, and they are valuable for the information they contain as well as the interpretations they offer. But we might as well face the fact that we cannot take in two or more themes simultaneously.

The two cycles of medicine at Harvard described in Appendix *iii* give a most intimate and critical commentary. Dr. Warren's reminiscences conclude a sixty-year cycle, from 1846 to 1906, and the present cycle is still with us. Proper emphasis is given to the fact that the great hospitals today are social newcomers, contemporaries of the movies and the airplane. It is surprising that, despite the fact that for a long time neither the Massachusetts General Hospital nor Harvard University accepted responsibility for medical education, the concern of the professors, who were also frequently chiefs of clinical departments, was such that medical education did not suffer as it might have if either the teaching or the care of patients had been in the hands of those to whom the combined careers were not congenial. There is an excellent discussion of the changing focus, emphasis, and, indeed, the changing scope of medical schools, the shifting of departmental organization, the development of the task-force approach to medical treatment, and the multiple allegiances and fragmented loyalties of people in the basic sciences who are working in clinical departments. Light is thrown on many other problems which vex the person who tries to determine whether the prestige, money, and satisfaction of clinical research versus "basic" research is an overstressed and unimportant item or whether the philosophic differences reveal a real separation into distinct entities. In this period of academic unrest and turbulence, Churchill's lucid and searching commentary on such problems at Harvard give us a scholarly critique from which any medical teacher might learn much. If at times the manner is a bit frosty, the somber tone is appropriate for the serious matter of Churchill's interpretation and Warren's chronicle. Neither lets solemnity become corrupted in pomposity. This book makes an interesting companion volume to Chesney's second volume on The Johns Hopkins Hospital and Medical School.

WILLIAM B. BEAN, M.D.

Selected Papers of Sir Gordon Holmes. Edited by F. M. R. Walshe. Price, 20 s. Pp. 262, with many illustrations. Macmillan & Co., Ltd., 10 St. Martin's St., London, W. C. 2, 1956.

Jackson, Parkinson, Holmes, Sherrington, Horsley, and Walshe are names chosen more or less at random to illustrate the high quality of the English school of neurology. The

task of selecting papers to celebrate the eightieth birthday of Sir Gordon Holmes presented to Sir Francis Walshe an extremely difficult task, for in neurology his name is written large. Clinical neurology has always held a fascination for those with keen analytical minds. Good observers, with the infinite patience to do careful and repeated neurological examinations and follow the natural history of disorders of the nervous system to their final outcome, have deciphered the relationship between lesions and abnormal signs and symptoms. One of the few useful medical by-products of recent wars has been the multitude of patients with a great variety of penetrating wounds of the head. Information from such sources, pieced out from careful studies, has clarified a great many puzzles and extended the field of clinical neurology to the point where it comes closer to being an exact science than any other discipline of medicine.

The contributions which Walshe selected are divided into three parts: papers on the cerebellum, papers on the cortical representation of vision, and papers on visual orientation and attention. They represent but part of the great accomplishment of this physician, investigator, and teacher. His own credo can be summed up best in his words on the occasion of the opening exercises of the Montreal Neurological Institute, in 1934: "If I were asked to select a motto, or a creed, for this new Institute, I could do no better than copy out Francis Bacon's statement of his scientific attitude, written more than three hundred years ago. 'For myself I found I was fitted for nothing so well as for the study of Truth; as having a mind nimble and versatile enough to catch the resemblance of things (which is the chief point), and at the same time steady enough to fix and distinguish their subtler differences; as being gifted by nature with desire to seek, patience to doubt, fondness to meditate, slowness to assert, readiness to reconsider, carefulness to dispose and set in order; and as being a man that neither affects what is new nor admires what is old, and that hates every kind of imposture.'"

A large part of the knowledge of function and disease of the central nervous system has come from Holmes' embodiment of these attributes. Walshe's selection of this group of papers illustrates why.

WILLIAM B. BEAN, M.D.

Young Endeavour. By William Carleton Gibson, D.Phil., M.D., C.M. Price, not given. Pp. 292, with 9 plates. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

There seems to be no question that productivity conditioned upon inspiration and discovery has been, if not the exclusive business of youth, at least one of its natural prerogatives. In different fields of endeavor the timing may vary. Superior performances in the physical sciences come perhaps a decade earlier than in the biological sciences. Despite the fact that an occasional person is still productive and a rare one creative after the middle years of life, the weight of experience and observation is with William Osler, whose emphasis of this point in a playful allusion to an arbitrary termination of activity in "The Fixed Period" address, brought down upon his head the howls of an outraged reading public fed upon the yellow journals of the day. Despite Sir Clifford Allbutt's championing of the older physician and contributor, the essential truth of the accent on youth has never been successfully denied.

William Gibson, in this very pleasant book "Young Endeavour," tell us the story of creative work, investigation, and discovery by undergraduate medical students during the last four hundred years. He cites examples of the work done as undergraduates by many who later went on to make even more distinguished observations and contributions. The topics of the book are arranged alphabetically, running the gamut from anesthesia to physics and optics. It is a commentary on our use of words that the term medical student has come to mean *undergraduate* medical student despite the fact that doctors who continue to be effective must be perennial students. A number of illustrations add to the zest of the book. Serving as illustrations in many places are quotations set apart from the text but bearing on the subject under consideration.

There are a few rather awkward statements, such as, "The acromegalic patient had secreted within the pituitary fossa in the base of his skull a tumor resembling a hen's egg in size." "Every student knows Romberg's name in connection with the loss of the erect posture with the eyes closed in certain ataxic disorders." Also, Brown-Séquard did not hold a chair at the University of Virginia but at the Medical College of Virginia, at Richmond. Distinguishing the location of medical schools in a state that has more than one seems to be almost impossible except for natives. But these are minor specks which should not detract from interest in a

book which should be an inspiration to medical students from twenty to eighty and a great stimulus to those who are intending to go into the profession of medicine.

WILLIAM B. BEAN, M.D.

5-Hydroxytryptamine. Edited by G. P. Lewis, Ph.D. Price, $9.50. Pp. 252, with many illustrations. Pergamon Press, Inc., 4 & 5 Fitzroy Sq., London, W. 1, 1958.

In the ten years since sertonin, or 5-hydroxytryptamine, came out of its obscurity as a mysterious pharmacological force it has had much attention in clinical medicine and in pharmacology. All manner of studies have been done. Yet the surprising point, so excellently illustrated in this report of a symposium held in London, in April, 1957, is that not only its actions but its modes of action are still in dispute. Where it is manufactured, how it is transported, what lets it into cells, lets it out or keeps it in, and many other problems are as mysterious now as they were when serotonin first was discovered. Some of the many paradoxical effects of serotonin are clearly discussed and outlined in the individual essays of this symposium. A considerable distance separates what can be learned in an experimental laboratory and the clinical problems we encounter in sick patients. Monoamine oxidase, coagulation, vasomotion, and activity of nerve tissue exhibit more problems than average. One has the sensation in this field that we are at the stage of confusion which heralds clarification. I hope so.

As much as anything else, this book illustrates the complexity of most biological problems and the difficulty of devising the proper experiment to solve them.

Certain scientists, educators, and investigators maintain that the future of medicine lies, if not wholly at least mainly, in the laboratory—that we can understand disease only by probing into the intricacies of energy exchange, enzyme activities, and so on. The story of serotonin illustrates in very graphic fashion the need for clinical research to be developed in its own right. As a biologic discipline, it looks for help in its problems wherever it may be found, not in a single basic science. The physical effect of serotonin was a plague in physiological and pharmacological perfusion experiments because defibrinated or clotted blood contained an enormously potent vasoconstrictor not active in unclotted blood. The intense vasoconstriction would shut down the blood vessels of a perfused organ unless the blood had first been perfused through the lungs. But this material, such a nusiance in experimental work, did not effectually excite the curiosity of those who encountered it in their daily experiments. Its discovery, achieved in Page's laboratory, resulted from an effort directed toward solving the clinical problem of hypertension. At about the same time Erspamer found that it was his "enterotonin."

Perhaps the spirit which expresses most vividly the present state of our understanding of the actions of serotonin may be taken from a summary comment of Brodie, who says: "it is not, like most body substrates, randomly distributed throughout the body. . . . In physiology, as examples, beating of the heart and the gastric secretion of acid cannot be related to known biochemical events. After playing a poker game for so many years without winning a hand we should suspect that the deck is stacked. Perhaps the difficulty is that consciously or unconsciously we have been working on the assumption of the 'universality' of enzyme systems, perhaps because to many it has been the 'only game in town.' Otherwise, why do we keep on trying to explain the effect on one drug after another by its effects on oxidative phosphorylation? When morphine relieves pain is it not logical to think that it is affecting some quite specific mechanism in the brain? It is hard to imagine that if a substance is upsetting oxidative phosphorylation in the brain that it would not be doing so in other tissues as well."

WILLIAM B. BEAN, M.D.

Die medikamentöse Behandlung der Schilddrüsenerkrankungen. By Prof. Dr. W. Grab, and Prof. Dr. K. Oberdisse. Price, DM 39.60, $8.40. Pp. 292, with 36 illustrations. Georg Thieme Verlag, Herdweg 63, (14a), Stuttgart N, 1959.

This short volume, dealing with the management of various thyroid disturbances, is arranged in two parts. The first part deals with the scientific background for the employment of diagnostic and therapeutic agents and is written by Dr. W. Grab, the director of the pharmacological institute at Giessen. The second part, dealing chiefly with clinical problems and usage of agents, is written by Dr. K. Oberdisse, director of the medical clinic at Düsseldorf. This is an up-to-date and excellent blend of scientific and clinical material.

CARL A. DRAGSTEDT

Regional Ileitis. By Burrill B. Crohn, M.D., and Harry Yarnis, M.D. Price, $7.50. Pp. 239, with 81 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1958.

This, the second edition of Dr. Burrill Crohn's monograph on regional enteritis, was written some ten years after the first. Dr. Harry Yarnis, an associate of Dr. Crohn's at the Mt. Sinai Hospital, is co-author. Since the first edition, no great advances have occurred in the diagnosis or in the treatment of regional enteritis, and no real clue to the etiology of the disease has been found. The publication of this second edition, however, is fully warranted as the number of observed patients has more than doubled and their follow-up has been extended a decade. A total of 676 patients with ileitis in one of its various types form the basis of the report. Some were included in Dr. Crohn's original paper on regional ileitis, in 1932, and thus have been followed for twenty-five years. All were private patients of Dr. Crohn and have been followed by him personally. Certainly his is a unique experience in this field.

The opening chapters cover the historical background, theories of etiology, and gross pathology well. Dr. Crohn believes that abdominal trauma may on occasion be an etiological agent and quotes cases from the literature as well as several of his own where this was a factor. The chapter on the clinical features of ileitis is excellent, probably the most interesting portion of the book. It is packed with tabulated data as well as interesting observations on the various facets of this disease. The most disappointing part of the work is the discussion of medical treatment. This may well reflect the fact that therapy is rather disappointing. I do not believe, "In all cases, intramuscular injection of crude liver extract and of vitamin B complex, 2 cc. of each, should be given into the buttock every other day." Neither do I think, "Synthetic vitamin K is indicated in all instances of hemorrhage from the bowel wall . . .," or, "Five to fifty milligrams of synthetic vitamin K daily . . . should, as in ulcerative colitis, control the hemorrhagic manifestations." Otherwise, the treatment advocated is the standard fare of diet, insoluble sulfonamide, and rest. The authors are cautious in their endorsement of the use of the adrenal glucocorticoids.

In contradistinction, the discussion of the surgical treatment of the disease is excellent. The controversy of short circuiting versus resection is examined from all aspects. The authors favor short circuiting with ileal transection, and their figures indicate that this is the better form of surgical treatment. A lower operative mortality rate is the most impressive item which is presented to support the claim of superiority of the bypass procedure.

Dr. Richard H. Marshak and Dr. David A. Turner contributed excellent chapters on small intestinal radiography and intestinal absorption, respectively.

Dr. Crohn has had the unparalleled opportunity to follow personally hundreds of patients with this disease over a period of many years. Fortunately he and Dr. Yarnis have published their observations in this fine monograph. All physicians who have patients with disease of the gastrointestinal tract should enjoy reading this little volume on Crohn's disease.

JAMES A. CLIFTON, M.D.

Snoring as a Fine Art and Twelve Other Essays. By Albert Jay Nock. Price, $3. Pp. 196, with no illustrations. Richard R. Smith Publisher, Inc., Rindge, N. H., 1958.

The mark which Albert Jay Nock left has increased rather than faded since his death. Like fine mellowed wine, it has rare savor. He was the creator of a distinguished and distinctive style. It has been used as a model by many who unfortunately fall short of achieving his salty combination of smooth flowing English, enormous vocabulary, and frequently arresting and disturbing statements which jar one from the simple relaxed pleasure which comes from reading such prose. His heavy-handed irony stopped short of bleak cynicism. His realism, though harsh and rocky at times, escapes the desperate and depressing reaction of pessimism, and his choice of words constantly bears testimony to his admission that he read the dictionary for sheer pleasure. He is not above using teeth-rattling expressions to dislodge the reader from his complacency. As an example, he said, "'*The* French' means nothing but '*Them* French' sums up the whole situation at a glance.'"

In our hurried society the more leisurely approach of the essay is fast going out of style. Anyone who reads Nock's essays realizes the great loss it is that this is true. Though a lucid and pleasing style is valuable and indeed essential to the art of great essay writing, mere literary style may cover up for a lack of substance in writing and thinking. Not so with Nock, in whose work one senses a profound grip on the truth and an approach to reality

which is achieved only by those who can carry excellence to the point of greatness. One feels in Nock the grip of a keen and penetrating intellect, shorn of most of the prejudice which so besets us, standing on its own and facing some unpleasant facts of life without demoralization.

The essay "Snoring as a Fine Art," with its beguiling and somewhat misleading title, deals with the massive, instinctive, almost animal-like ability of the famous Russian general Kutusov to predict the utterly illogical course which Napoleon would take after the sack of Moscow to lead his army to annihilation in a perverse series of moves, which revealed the complete breakdown of his hitherto distinguished military genius. It is really a study of inspiration in the intuitive mind. The timelessness of some of the essays is indicated by the fact that, though most of them were written in the 1930's, they bear on our problems today with startling immediacy. From each of the essays in a different way there is a great deal to be learned. It might spoil the fun if a discussion of their substance was given here.

Not only was Nock a great essayist and a critic of the times, but he was a true historian and a scholar whose profound thinking and erudition he himself treated with disarming humility, almost with surprise. In our day of confused and slightly panicky assaults on our educational lapses of the past (a frightening reappraisal), it would be well to consider Nock's book, "The Theory of Education in the United States," in which he said: "The educable person, in contrast with the ineducable, is one who gives promise of some day being able to think: and the great object of educating him, of subjecting him to the Great Tradition's discipline is to put him in the way of right thinking, clear thinking, mature and profound thinking. Now, the experienced mind is aware that all the progress in actual civilization that society has ever made has been brought about not by machinery, nor by political programmes, platforms, parties, not even by revolutions, but by right thinking." Certainly Nock himself exemplified and embodied his own admonition in a unique way.

One of the most delightful autobiographies I know is Nock's, "The Memoirs of a Superfluous Man," and my delight in it has been shared by a host of readers. In fact its remarkable popularity so surprised Nock, who was pretty generally neglected on best-seller lists, that he remarked that there must have been something wrong with it. Such was his suspicion of taste in contemporary America.

Nock's brilliant biographies of Henry George and Thomas Jefferson, his "A Journal of These Days," "Our Enemy the State," and his "Life of Francis Rabelais," together with his essays and the splendid work he achieved when he was editor of *The Freeman*, have properly gained him an international reputation and a still growing recognition of his supreme achievements as a master of English prose and of wise thinking. Too salty for some, too free from wishful thinking to be read with comfort, his critical and creative faculties, balanced but fearless, make him an essayist who could help us think straight and then act wisely and fearlessly. In this regard he much resembles another incomparable essayist, the biologist William Morton Wheeler, nearly forgotten in the pressures of our wasteful haste .

WILLIAM B. BEAN, M.D.

Cardiovascular Diseases. Third edition. By David Scherf, M.D., F.A.C.P., Professor of Clinical Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and Linn J. Boyd, M.D., F.A.C.P., Professor and Director of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals. Price, $17.75. Pp. 829, with 119 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; and 99 Great Russell St., London, W. C. 1, 1958.

The authors have again succeeded in presenting in an interesting and readable manner a text covering the broad field of cardiovascular diseases. The clear, orderly, detailed format of the earlier edition is unchanged. The length, however, has been almost doubled in the process of revising, with the inclusion of the additional knowledge accumulated during the intervening decade. Those who enjoyed the informal, conversational style of the preceding edition, flavored by the author's personal comments consequent to their long and wide clinical experience, will be pleased to find it continued.

Insofar as medicine in many respects is indeed an art, it is inevitable that in a work of this large a scope some will find points with which they do not agree. For example, the sweeping claim that "definite relief" of the pain of acute hepatic engorgement follows the proper use of the leeches "in every instance" will find some disbelievers, if only on the basis of its claimed infallibility. The statement that venesection for cardiac asthma and pulmonary

edema is "empirical treatment like cupping and for which (beneficial results) no satisfactory explanation is available" is somewhat surprising, as is the subsequent statement that following venesection "there is no proof that the amount of circulating blood diminishes!" The problems of atherosclerosis are well discussed in several chapters; however, the classification of arteriosclerosis in a brief two-and-one-quarter-page chapter is unclear and confusing.

Perhaps the disturbing number of incidents where singular nouns are used with plural verbs and conversely, as well as the misspelling of a few words, is ascribable to the foreign printing. I, disappointingly, received a copy to review in which eight pages were blank.

In general, however, these objections are not great, and it can be said that here is a worth-while book which covers the field, contains approximately three thousand references, and should prove helpful to student, practitioner, and specialist.

DAVID C. FUNK, M.D.

Myasthenia Gravis. By Kermit E. Osserman, M.D., F.A.C.P. Price, $10. Pp. 286, with 58 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1958.

This volume presents the current concepts of the pathological physiology, diagnosis, and management of myasthenia gravis. Controversial points are fairly presented together with the author's opinion. The book should be useful to the physician confronted with the management of the myasthenic patient. There are extensive references to the literature, and the text is well indexed.

RICHARD J. JOHNS

Cardiovascular Sound in Health and Disease. By Victor A. McKusick, M.D. Price, $15. Pp. 570, with 494 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

A scientist of the last century was reputed to have remarked that until biology records data in visual form its place in science may be questioned. Dr. McKusick's work converts the information of the honorable art of auscultation into visual form.

To any physician using a stethoscope, this book will be useful. To one especially interested in diseases of the heart, its information is vital. For any teacher of physical diagnosis, it is mandatory.

The major part of the book records the author's unique experience of several years of recording heart sounds by the spectral phonocardiogram. The parameters of time, pitch, and intensity are well displayed for study in this method of recording data. In addition, full references to the work of others using standard sound recording devices and illustrations of their recordings are present in the book.

A most interesting and pleasantly written chapter on the history of cardiovascular sound introduces the topic. Sprinkled throughout the book are many bits of information, ancient and recent, of interest to auscultation. Ninety-two pages are devoted to an excellent discussion of basic considerations of cardiovascular sound. A most valuable chapter on pulmonary sound phenomena is included in the book. A technical section is appended.

As the cardiovascular surgeon has expanded his scope he has uncovered embarrassing areas of ignorance in the cardiologist's concepts. The use of sound tracings prevents our building a house of cards based on auscultation. Already many cherished notions have had to be discarded and many confusing aspects of auscultation have been clarified by sound tracings. In addition, sound recordings have unexpectedly proved to be of help in evaluating the very conditions of interest to the surgeons. This is particularly so in lesions of the mitral value.

In day-to-day ward work, recordings have proved most useful in demonstrating and clarifying extra heart sounds. The time intervals of some of these bear a relationship to flows and pressures in the heart, and sound tracings provide easily obtained information about these. The relationship between sound phenomena and left atrial pressures in mitral stenosis is a fairly accurate one. The interval between the atrial gallop sound and the first heart sound relates to left ventricular function. The effect of respiration on the splitting of the second heart sound at times exhibits a neat relation to function of the right ventricle. Perhaps other interesting relations between physiological events and sound may be disclosed in the future.

Regarding murmurs, it is most unfortunate that many internists and residents still believe the recording should be used to settle the bedside dispute whether a murmur is or is not

present. In this respect, the tracings have limited value. They do, however, have considerable value in recording the shape of a systolic murmur, to determine whether it arises from the mitral or aortic value. The pattern of the murmur may also be of some help in the vexing matter of "organic" versus "functional" murmurs. Some clue as to the severity of stenosis in aortic and pulmonary valve lesions may be gained from study of sound tracings. The effect of respiration on the intensity of the murmur is a useful point that can be visualized in studying murmurs thought to arise from the tricuspid valve.

The bibliography is most rewarding. More than sixteen hundred references are cited, and full titles are used for each citation. The book is a tribute to the energy and scholarship of the author. Words are used accurately, and the terms chosen seem justified. Illustrations and tables are appropriate, helpful, and of good quality. Errors in proofreading are minor and not distracting. It is a definitive work on this topic and may remain the standard references for many years.

ANDREW KERR JR., M.D.

Psychotherapeutic Drugs. By Ashton L. Welsh, M.D., Assistant Professor of Dermatology and Syphilology, University of Cincinnati College of Medicine. Price, $4.75. Pp. 139, with no illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

A book that provides information on most of the current tranquilizing drugs has been much needed. In the face of the constant barrage of monthly "discoveries" in this field, this book is as up to date as one could hope. It is, however, disappointing to learn that the book has been written by a dermatologist primarily for dermatologists. Consequently, while it is very adequate for this purpose, it is definitely lacking for physicians in other fields. The description of clinical uses is sparse and repetitious and does not provide a sufficient basis for the application and comparison of the relative merits of different drugs. While all complications and side-effects are listed, there is almost no discussion of their frequency and seriousness. The book confines itself to tranquilizing drugs, which was the author's intent, but the broad title, "Psychotherapeutic Drugs," might lead one to hope for an inclusion of the every-growing group of drugs for depression, represented by Iproniazid and, more recently, Imipramine. A discussion of and comparison with the sadly neglected and underrated old standbys, such as the barbiturates, bromides, and the amphetamines, would also have been most welcome.

In spite of these limitations, until a more comprehensive work is written on the subject, the book does provide a useful guide through the maze of tranquilizers that confronts and confuses us today.

A. S. NORRIS, M.D.

Tumors of the Lungs and Mediastinum. By B. M. Fried, M.D., F.C.C.P. Price, $13.50. Pp. 467, with 340 illustrations. Lea & Febiger, 600 Washington Sq., Philadelphia 6, 1958.

This well-written and beautifully illustrated book deals with practically all aspects of neoplastic disease of the intrathoracic organs, exclusive of neoplasms of the esophagus. The author's wide experience is reflected in the thoroughness and the lucid description of the pathology of the different neoplasms and its correlation with the clinical findings and treatment. The first half of the book is given to the ever-increasing problem of bronchogenic carcinoma. The histopathology—possible causes of the disease, clinical manifestations, and the pattern of metastasis—is thoroughly described and illustrated, including case reports, roentgenograms, charts, and photomicrographs. Drs. Arnold L. Bachman, Roger H. L. Wilson, Seymour M. Farber, Thomas H. Burford, Thomas B. Ferguson, and Harold W. Jacox contributed chapters discussing radiologic diagnosis, pulmonary functions, surgical treatment, and x-ray therapy. The less common tumors of the lungs and pleura are also fully discussed. The second half of the book deals with neoplasms of the mediastinum, in a short and precise manner. A well-chosen, extensive bibliography is attached to each chapter of the book and makes it very valuable from the standpoint of reference and further reading. The constant emphasis throughout the book on correlation of clinical and pathologic findings makes it valuable for all physicians interested in chest disease. It also should be of great value to the general practitioner, who will find this an excellent reading and reference book.

J. L. EHRENHAFT, M.D.

The Story of White Haven Sanatorium: A Memorial to Dr. Lawrence F. Flick. By Frank A. Craig, M.D. Pp. 76. Privately printed by the Board of Trustees of the Jefferson Medical College and Medical Center, Philadelphia, 1959.

Modern Chemotherapy of Tuberculosis. By Roger S. Mitchell, M.D., and J. Carroll Bell, M.S. Price, $4. Pp. 109. Medical Encyclopedia, Inc., 30 E. 60th St., New York 22, 1958.

By chance these two volumes arrived together; between them one has a panorama of the treatment of tuberculosis in America between 1895 and 1958. "The Story of White Haven" is a highly personal memoire, written by Frank A. Craig about his old sanatorium and his mentor, Lawrence F. Flick. Flick was one of a number of the unsung heroes of the early antituberculosis campaign. A man of vision, zeal, and dogged determination, which his enemies called "stubborness," he founded the first state Tuberculosis Society in America (Pennsylvania, 1892), the Rush Hospital (1895), the White Haven Sanatorium (1901), and the Henry Phipps Institute (1903) and was one of the founders of the National Tuberculosis and Health Association (1904). Dr. Craig's reminiscences recall many of the struggles, mistakes, defeats, and triumphs of the early sanatorium and of the zealous physicians who led the way.

We see old photographs of hardy patients "taking the cure" at twenty-eight degrees below zero. Because of the "Alp Complex," which started in Europe and was encouraged by Trudeau's success at Saranac Lake, the early American sanatoria were all built on the highest and most inaccessible parcels of real estate. The unfortunate states that could not find at least a medium-sized mountain used their driest deserts. The highly touted isolation of the sanatoria has contributed largely to their downfall. One by one they have closed their doors or changed their status. With typical American enthusiasm, many sensible things were overdone. Fresh air was beneficial, ergo, living in tents and barns must be extra beneficial. Adequate nutritution of emaciated patients was a proper goal, but Flick's poor consumptives were forced to ingest twelve glasses of milk plus six raw eggs a day, plus one meal of meat, vegetables, and dessert. How fortunate that lipids and cholesterol had not yet become dirty words! Rest, air, food, and informal psychotherapy, in the form of a very strong doctor-patient relationship, constituted total treatment fifty years ago, and many patients survived the treatment and the disease.

The old sanatoria developed into centers of education as well as treatment. Patients, nurses, neighboring physicians, and eventually graduate students all acquired knowledge of the ramifications and vicissitudes of tuberculosis.

Many doctors came first as patients. Having arrested their own tuberculosis, they stayed in the field of pulmonary disease and made important contributions to medicine. This source of supply has largely dried up in the United States. The surviving sanatoria can no longer depend on young physicians with " a touch of TB" to come and work for a year or two.

Temporary collapse, permanent collapse, and the complications of both procedures were sanatorium-oriented modalities. In just over a decade the era of chemotherapy and resection has sounded the funeral bell for the isolated institutions.

"Modern Chemotherapy of Tuberculosis," by Mitchell and Bell, is the eleventh of a series of Antibiotics Monographs. An excellent summary of a vast field, this volume covers all elements of the pharmacology and clinical application of antituberculosis drugs. Streptomycin, aminosalicylic acid, and isoniazid are properly considered the major, or standard drugs; a score of "second choice" and experimental compounds are considered. The authors have wise thoughts on drug regimens, bacterial resistance, drug reactions, and ancillary measures required for complete treatment. They realize far better than do many of their fellow physicians that tuberculosis is still a complicated disease. In many ways the treatment is more difficult today than it was fifty years ago. Certainly the results are better today, but they are not as good as they should be.

Too many physicians and public health agencies behave as though all that is needed for total treatment of tuberculosis is a bottle of pills. The careful reader of Mitchell and Bell's excellent monograph will realize that pills alone are not sufficient. Treatment should be started in a hospital equipped to do refined bacteriologic studies, to recognize and treat drug reactions should they occur, and to start educating the patient. After two or more months, if all goes smoothly and a responsible patient has an adequate home, continuation of supervised therapy at home should be considered. There must be opportunities for periodic reevaluation

of the patient and his disease. Changes in therapy and termination of treatment are serious decisions, to be made only after careful evaluation of data. Proper selection and timing of surgical procedures also depend on complex factors in the life cycle of the patient and his disease.

Granted that our present tools are not perfect, a wide application of the tools and knowledge available today would ensure significant improvement in our results.

ROBERT V. COHEN, M.D.

A Short Practice of Surgery. By Hamilton Bailey, F.R.C.S. (England), F.A.C.S., F.I.C.S., F.R.S.E., and McNeill Love, M.S. (London), F.R.C.S. (England), F.A.C.S., F.I.C.S. Price, 4 £ 4 s. net. Pp. 1389, with 1,697 illustrations (285 colored). H. K. Lewis & Co., Ltd., 136 Gower St., London (printed in Great Britain for H. K. Lewis and Co., Ltd. by Hazell Watson and Viney Ltd., Aylesbury and Slough), 1959.

The title is surely a misnomer; this is not so short a "practice of surgery." The authors attempt to cover all of clinical surgery, including subspecialties, such as cardiopulmonary, otolaryngology, urology, and orthopedics. The effort to provide "something for everybody" has not been fully successful. The text tends to be elementary and superficial and will be of little use to qualified surgeons. Most discussions of diagnosis and treatment are consistent with current informed thought, although some are belabored and irrelevant. An example of this is the section on infections in general, tuberculosis in particular. Graphic and photographic illustrations are plentiful and usually clarify the text. The techniques of a well-chosen group of operations are briefly described and will be useful to the medical student but not to the experienced surgeon. The absence of documentation and bibliography further reduces the usefulness of this text to the trained physician. British rhetoric helps to make the text interesting, but the glossy single-column format is more tedious to read than the common two-column format of current American texts. This book is recommended to the medical student.

JOSEPH BUCKWALTER

Medicine and Man. By Ritchie Calder. Price, 50 cents. Pp. 256, with no illustrations. The New American Library, 501 Madison Ave., New York 22, 1958.

This paperback book by a well-known British science writer gives a good running synopsis of the background of many modern developments and practices in medicine. The style, though breezy, is not objectionable. The matter as well as the manner is sound. Only a few minor errors were noted. It would have its greatest appeal for those who are thoroughly ignorant of medical history, although it is not likely to offend someone whose knowledge is deep as well as wide in such areas. Its main value is as a guidebook for further investigation and study. It could be very helpful to the undergraduate student who is thinking of a career in medicine.

WILLIAM B. BEAN, M.D.

The Plasma Proteins. By Paul G. Weil, B.A., M.D.C.M., M.Sc., Ph.D. Price, $3.50. Pp. 133, with 2 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1959.

A tremendous series of papers concerning the nature, properties, methods of determination, and clinical significance of the plasma proteins has accumulated during the past twenty years. Several review articles have described changes in plasma and serum proteins in disease. The present monograph is an attempt to bring together as many of the facts as possible dealing with the clinical significance of the plasma proteins. Within the limits of size and scope, it should be of value to physicians, interns, and students. By the elimination of specific details of methodology and of references to the literature, the author has been enabled to condense considerable information in this small volume. Variations in albumin, fibrinogen, and globulin components in a multitude of diseases have been described. The role of each of the plasma protein components in closely related diseases has been rather thoroughly explored. The major shortcoming of the book, which is readily apparent to a research worker in this field, is the lack of organization of the material. It is realized that every author is entitled to his own opinion regarding the organization of the material he is presenting, but the temptation to reorganize the contents of this monograph is very strong.

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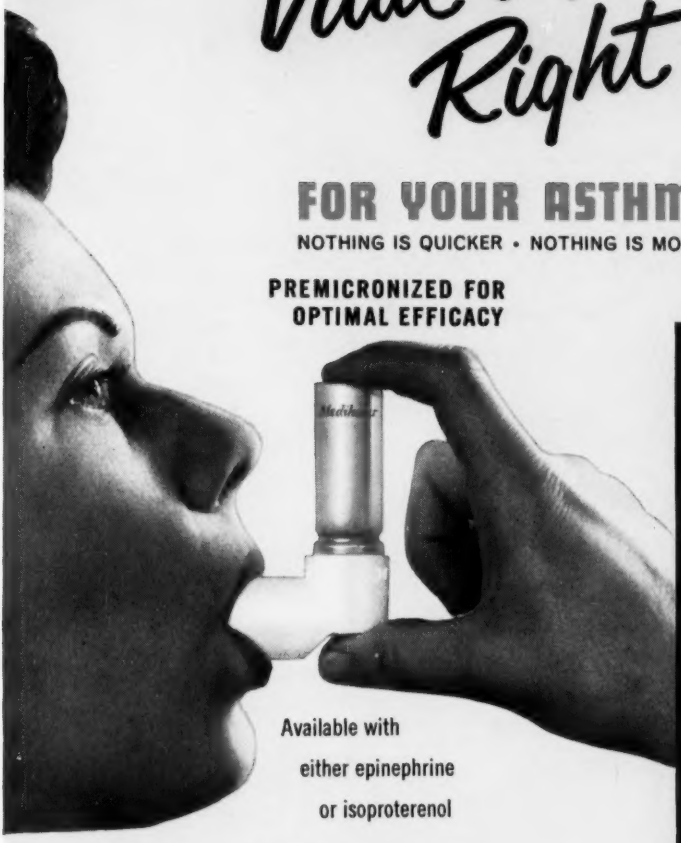

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